The Development of Palladium(II)-Catalysed Auto-Tandem and Desymmetrisation Reactions

Claire Jane Campbell Lamb

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Abstract

This thesis outlines the work undertaken by the author on two projects, focusing on the development of Pd(II)-catalysed desymmetrisation coupling reactions.

Chapter one reviews literature pertaining to Pd(II)-catalysed coupling reactions, more specifically the oxidative Heck coupling reaction, its initial development and advancement. The related Pd(II)-catalysed conjugate addition reaction is also briefly discussed.

Chapter two describes the successful development of a Pd(II)-catalysed auto-tandem reaction, where the same Pd(II)-catalyst was utilised for both a dehydrogenation reaction and an oxidative Heck coupling reaction in one-pot. 2,2-Disubstituted cyclopentanediones were first dehydrogenated to the corresponding enedione before an oxidative Heck desymmetrisation reaction. The racemic reaction was investigated in both batch and continuous flow, as well as a batch and telescoped approach for the enantioselective reaction.

Chapter three outlines the pursuit to desymmetrise more complex *meso*-cyclic systems, which contain up to five-contiguous stereocentres, utilising Pd(II)-catalysis. An efficient protocol was developed to desymmetrise *meso*-polycyclic cyclohexenediones under mild Pd(II)-catalysed conditions in good yields and excellent enantiomeric ratios.

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Contents

Abbreviations

AcOH	Acetic acid
APCI	Atmospheric-Pressure Chemical Ionisation
Ar	Aryl group
ATC	Auto-tandem catalysis
ASAP	Atmospheric solids analysis probe
BIAN	Bis(imino)acenaphthene
(*R*)-BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
R)-MeOBIPHEP	(*R*)-(+)-2,2′-Bis(diphenylphosphino)-6,6′-dimethoxy-1,1′-biphenyl
bipy	2,2’-Bipyridine
Bn	Benzyl
Bpin	Pinacol boronic ester
Boc	*tert*-butyloxycarbonyl
BOX	Bisoxazoline
Bu	Butyl
BQ	1,4-Benzoquinone
°C	Degrees Celsius
calc.	Calculated
Cbz	Carboxybenzyl
conv.	Conversion
d	Doublet
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCBQ	2,5-Dichloro-1,4-benzoquinone
DCE	Dichloroethane
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DMA	*N*,*N*-dimethyl acetamide
DMF	N,N-Dimethyl formamide
dmphen	2,9-Dimethyl-1,10-phenanthroline
DMSO	Dimethylsulfoxide
dppp	1,2-Bis(diphenyphosphino)propane
d.r.	Diastereomeric ratio

EDG	Electron donating group
% e.e.	% Enantiomeric excess
eq./equiv.	Equivalent
e.r.	Enantiomeric ratio
Et	Ethyl
EtOAc	Ethyl acetate
EWG	Electron withdrawing group
FTMS	Fourier transform mass spectrometry
h	Hours
HRMS	High resolution mass spectrometry
Hz	Hertz
IBX	2-Iodoxybenzoic acid
IR	Infra-red
J	Coupling constant
m	Multiplet
M	Molar
Me	Methyl
MHz	Megahertz
min	Minutes
mM	Millimolar
mmol	Millimole
NMM	*N*-methylmorpholine
M.p.	Melting point
m/z	Mass-over-charge ratio
n.d.	Not determined
NMR	Nuclear magnetic resonance
5-NO_2-phen	5-Nitro-1,10-phenanthroline
NSI	Nanospray ionisation
OAc	Acetate
OTs	*para*-Toluenesulfonate
OTf	Trifluoromethanesulfonate
1,10-phen	1,10-Phenanthroline
Ph	Phenyl
Piv	Pivoyl
ppm	Parts per million

Pr	Propyl
PyOx	Pyridinooxazoline
q	Quartet
quant.	Quantitative
R	Alkyl/aryl group
Rf	Retention factor
r.t.	Room Temperature
s	Singlet
SPS	Solvent purification system
(*S*,*S*)-chiraphos	(2*S*,3*S*)-(−)-Bis(diphenylphosphino)butane
t	Triplet
TBAI	*tert*-Butylammonium iodide
THF	Tetrahydrofuran
Temp.	Temperature
TFA	Trifluoroacetic acid
TfOH	Trifluoromethanesulfonic acid (triflic acid)
TLC	Thin layer chromatography
TOF	Time of flight
UV	Ultra-violet

Chapter 1: Introduction – Palladium(II)-Catalysed Oxidative Heck and Conjugate Addition Reactions

1.1 Palladium Catalysis

The efficient formation of C–C bonds has been a difficult synthetic challenge for organic chemists. Emerging towards the end of the 20th century, palladium catalysis is a powerful and versatile route to forming C–C bonds and other important transformations within organic synthesis.[1] These reactions have since been employed as key steps within the synthesis of natural products, pharmaceuticals, agrochemicals and biologically active molecules in both academia and industry.[1] The wide reaching relevance and application of palladium(0)-catalysed C–C coupling reactions was aptly demonstrated through the award of the 2010 Nobel Prize in Chemistry to R. F. Heck, E.-I. Negishi and A. Suzuki for their work in this field.[2] Since the initial research conducted in the 1960s and 70s, the use of palladium(0) as a catalyst has blossomed.[1, 2] A wealth of C–C bond forming reactions are now available to synthetic organic chemists; including the works of Heck,[3, 4] Suzuki,[5] Negishi,[6] Stille,[7] Kumada,[8] Hiyama[9] and Sonogashira[10] amongst others.

In the early 1970s, Mizoroki[11] and Heck[4] independently published their work on palladium(0)-catalysed coupling of an unsaturated halide species with an alkene in the presence of base. The Mizoroki-Heck reaction (abbreviated to the Heck reaction in this review) has since become a very important carbon-carbon alkene-sp^2 bond forming reaction, and has been extensively employed in organic synthesis.[1, 2, 12] The popularity of this reaction derives from its advantage that only one of the coupling partners requires pre-functionalisation: an unsaturated halogen species couples with an alkene directly.

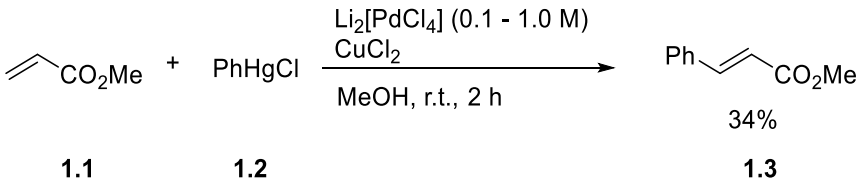
Numerous developments have taken place in the decades after the seminal work of Heck[4] and Mizoroki.[11] For instance, the Heck-Matsuda reaction involves the coupling of aryl diazonium salts with an alkene.[13] In 2001, Littke and Fu demonstrated one of the

first Heck coupling reactions with more readily available aryl chlorides at room temperature, with yields comparable to that of the aryl bromide.[14] Many other discoveries have been made on the back of the seminal work of Heck and Mizoroki.[1]

1.2 The Oxidative Heck Reaction

1.2.1 Introduction

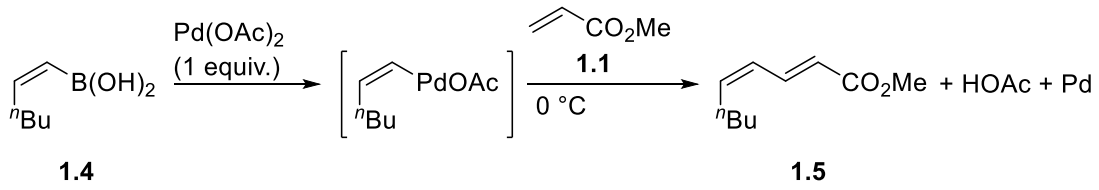
Prior to publishing his pioneering Pd(0)-catalysed work, interestingly, Heck investigated palladium(II)-mediated oxidative coupling reactions. In 1969, Heck reported a palladium(II)-facilitated coupling of arylmercuric salts **1.2** and acrylates **1.1** to form allylic aromatic compounds **1.3** (Scheme 1.1).[15] Several consecutive follow-on publications related to this work from Heck were also published.[3, 15-20] However, organomercurials are very toxic, and understandably, the latter research focused on the use of aryl halides in the development of the Heck reaction.



Scheme 1.1: Development of the palladium(II)-mediated coupling reaction

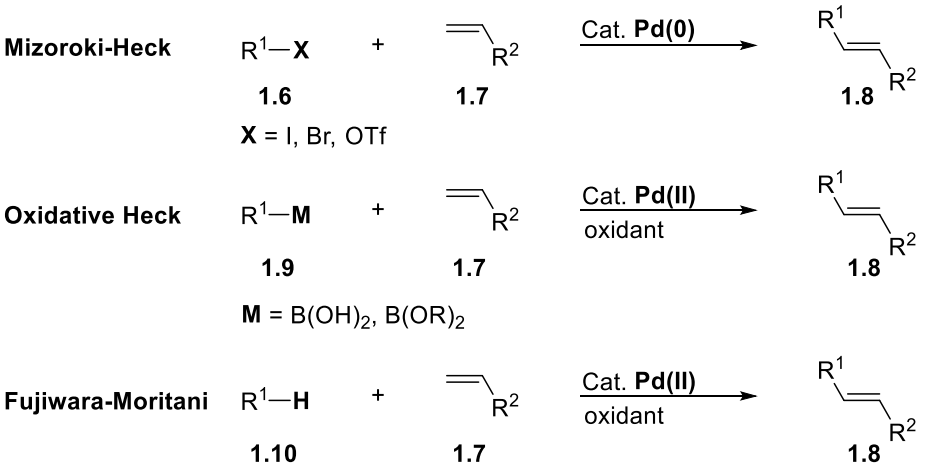
In 1975, Heck and Dieck reported further developments of a palladium(0)-catalysed coupling reaction, but in addition, they also disclosed the first palladium(II)-mediated *oxidative* Heck reaction involving the coupling of an alkenyl boronic acid **1.4** and an alkene **1.1** (Scheme 1.2).[21] Unfortunately, this work was stoichiometric in $Pd(OAc)_2$. Despite the potential of this early work, the Pd(0)-catalysed C–C bond forming was developed first.[4] Consequently, the Pd(II)-catalysed oxidative Heck reaction has not been investigated to the same extent as its Pd(0) counterpart. The oxidative Heck

reaction was rendered catalytic in 1994 in the pivotal work by Uemura and Cho.[22] Subsequently, over the past 20 years, significant improvements have been made to the oxidative Heck reaction and will be the focus of this review.



Scheme 1.2: First palladium(II)-facilitated oxidative Heck reaction with a boronic acid

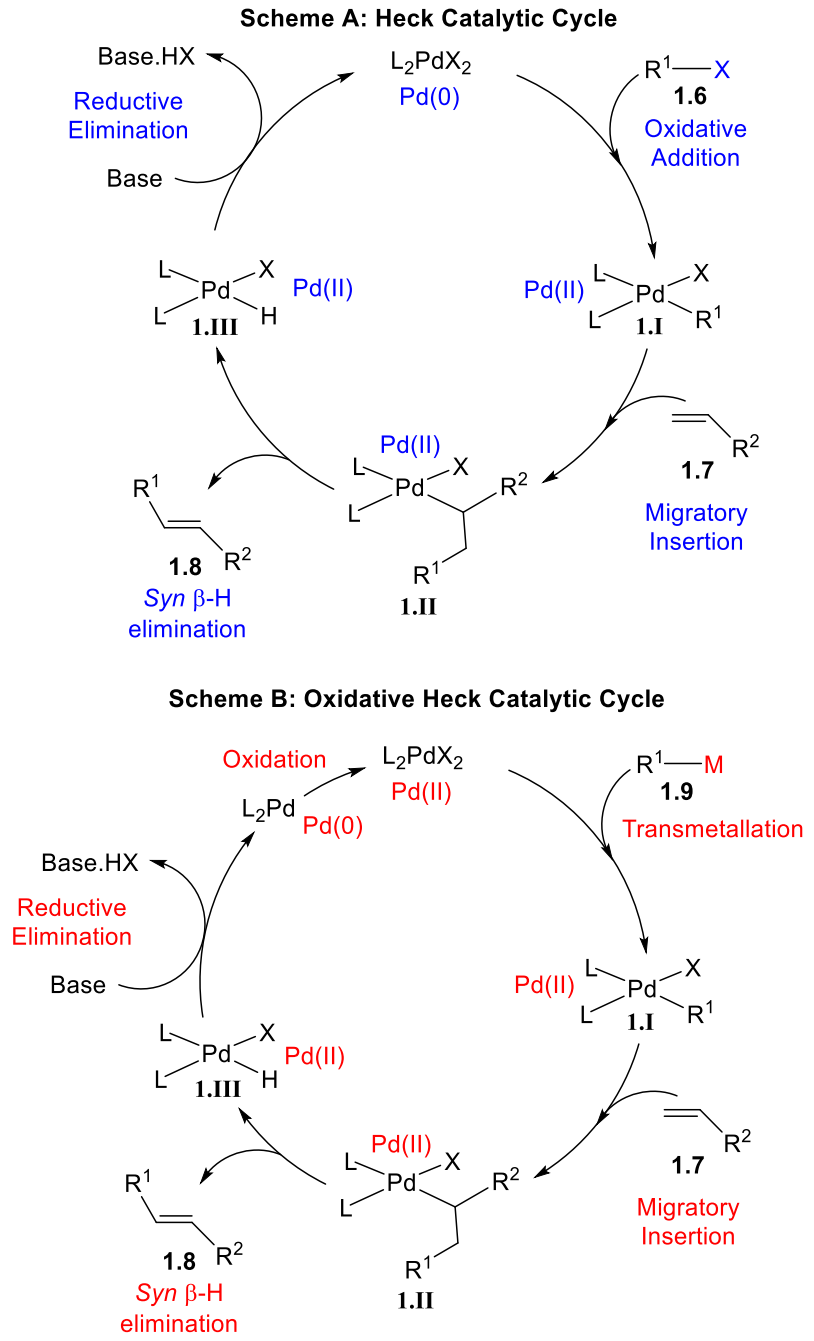
The oxidative Heck reaction is formally the coupling of an aryl or alkenyl-metal species **1.9** (typically an organoboron species) with an alkene **1.7** in the presence of a Pd(II)-catalyst and an oxidant (Scheme 1.3). In contrast, the Heck reaction is the coupling of an aryl or alkenyl halide **1.6** with an alkene **1.7** in the presence of a Pd(0) catalyst. The Fujiwara-Moritani reaction is another relevant noteworthy example of a Pd(II)-catalysed coupling reaction but will not be discussed within this literature review. Initially reported in the 1960s, the reaction involves the coupling of an arene **1.10** and alkene **1.7**[23, 24] and has gained popularity in recent years.[25-27]



Scheme 1.3: Difference between reagents employed in the Mizoroki-Heck, Fujiwara-Moritani and the oxidative Heck reactions

The differences between the Heck and oxidative Heck reaction extends further than the reagents employed (Scheme 1.3); they also differ in terms of mechanism, specifically the first step (Scheme 1.4).[28] The Heck reaction initiates with oxidative addition of the aryl halide or triflate **1.6** to form intermediate **1.I** (Scheme1.4A). The oxidative Heck reaction, on the other hand, commences with transmetallation of aryl organoboron species **1.9** onto the Pd(II)-catalyst to form **1.I** (Scheme 1.4B).[i] The cycles then proceed in an identical manner, migratory insertion of an alkenyl species to access **1.II**, followed by *syn-β*-hydride elimination from intermediate **1.II** to furnish coupled product **1.8.** Base facilitated reductive elimination from intermediate **1.III** regenerates the catalytically active Pd(0)-species within the Heck cycle. A further oxidation step is required to regenerate the Pd(II)-catalyst for the oxidative Heck cycle.

[i] The initial step of transmetallation is specific to the Pd(II)-catalysed oxidative boron Heck reaction. A related processed where the initial step is C-H activation, also Pd(II)-catalysed, is also called the oxidative Heck reaction or the Fujiwara-Moritani reaction.[31] Although related, this is a different reaction with another mechanism and will not be covered in this review.



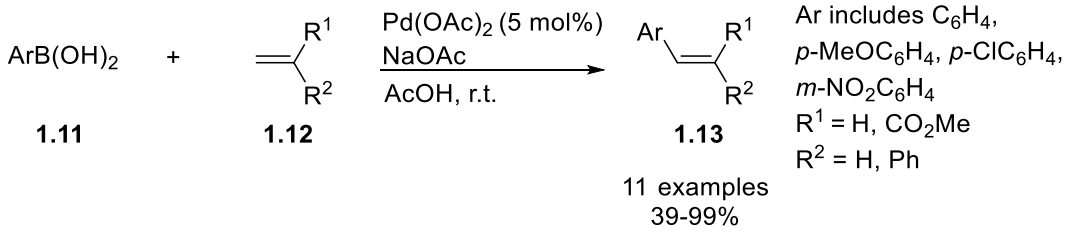
Scheme 1.4: Proposed mechanism for the Heck and oxidative Heck cycles[28, 29]

There are some considerable advantages of utilising Pd(II)-catalysed over Pd(0). The oxidative Heck reaction has shown itself to be more tolerant of di- and tri-substituted alkenes, and even cyclic substrates, all of which are reluctant to couple and form the Heck-type product under Pd(0) catalysis.[30-36] In modern times, environmental effects need to be taken into consideration when assessing the viability of a reaction, especially

if the reaction is to be scaled up for industrial use.[31] Utilising organoboron reagents, a widely commercially available coupling partner, bypasses the production of halide salt waste.[37] Moreover, a good functional group scope is often displayed, the reaction is tolerant of air and moisture, and frequently only requires mild reaction conditions.[30, 31, 34] As such, these general advantages have led to an increase in the employment of Pd(II)-catalysis in the formation of C–C bonds, and has been the focus of several review articles in recent years.[31, 38-40]

1.2.2 Development of the Oxidative Heck Reaction

As previously mentioned, a Pd(II)-facilitated coupling reaction was initially investigated by Heck in 1969[41] but was largely ignored until 1994, when Uemura and Cho developed catalytic conditions.[22] The group investigated the Pd(II)-catalysed cross-coupling of aryl and alkenyl boronic acids **1.11** with mono- and disubstituted alkenes **1.12** to access cross-coupled alkene **1.13** (Scheme 1.5).



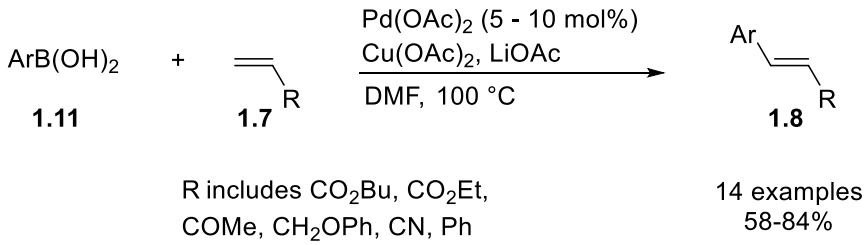
Scheme 1.5: The first reported catalytic oxidative Heck coupling reaction with aryl boron reagents [22]

Mild room temperature conditions were employed, with sodium acetate in acetic acid and catalytic amounts of $Pd(OAc)_2$ to furnish **1.13** in yields of up to 99%. In the absence of NaOAc as base, a yield of only 10% was recorded.

Uemura and Cho originally suggested that this reaction is Pd(0) catalysed. They proposed that the Pd(II) species is reduced to Pd(0), followed by a Heck-type catalytic cycle (see mechanism in Section 1.2.1, Scheme 1.4), and *oxidative addition* of the Pd(0)

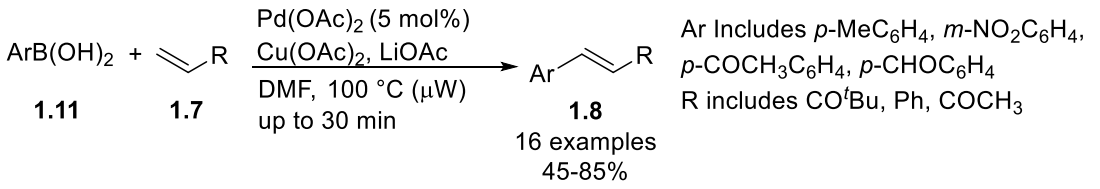
species into the C-B bond of the aryl boronic acid **1.11**. However, no mechanistic studies were carried out to prove this and many subsequent publications refer to this study as the first example of the Pd(II)-catalysed oxidative Heck reaction.

In 2001, Mori and co-workers investigated the cross-coupling of alkenes **1.7** with several different organoboron species (aryl boronic acids **1.11**, alkenyl pinacol boronic esters and tetraphenylborate) in the presence of an oxidant to regenerate the catalytically active Pd(II) species.[42] $Cu(OAc)_2$ was employed as the oxidant, LiOAc as the base in polar aprotic solvent *N*,*N*-dimethylformamide (DMF) (Scheme 1.6) to successfully couple both electron-withdrawing and -donating aryl boronic acids **1.11** with alkenes **1.7** (58-84% yields). Excellent *E*-selectivity was achieved with all substrates except for acrylonitrile, which produced an *E*:*Z* ratio of 3:1.



Scheme 1.6: Oxidative Heck coupling reaction employing $Cu(OAc)_2$ as an oxidant[42]

In 2003, Larhed and co-workers demonstrated the applicability of oxidative Heck chemistry to microwave irradiation with $Cu(OAc)_2$ as oxidant (Scheme 1.7).[43] Coupled product **1.8** was furnished in good yield and good *E*-selectivity. Pleasingly, electron-withdrawing and -donating functionalised aryl boronic acids **1.11** proceeded with moderate to excellent yields (45-85%).

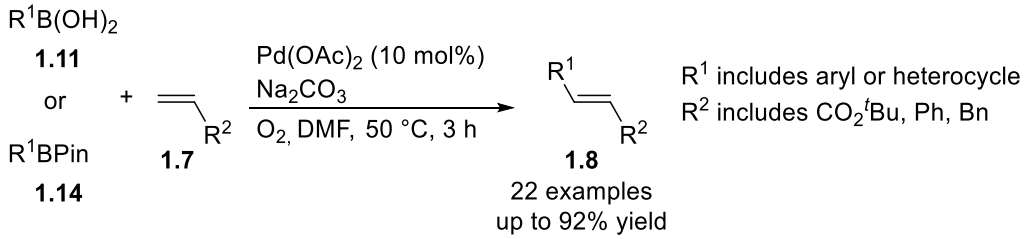


Scheme 1.7: Microwave assisted oxidative Heck coupling[43]

1.2.3 Molecular Oxygen as an Oxidant

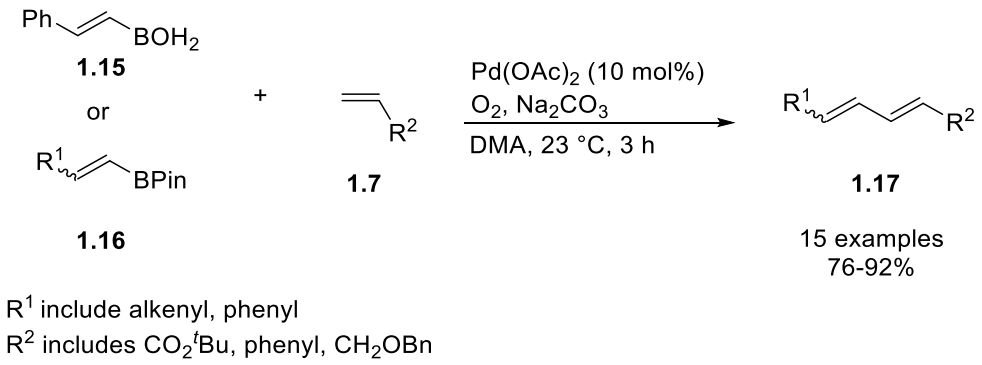
Several oxidants have been successfully employed in oxidative Heck coupling reactions.[31, 44] Amongst the most popular during early investigations were copper(II) salts[3, 17, 42] and benzoquinones.[45] In more modern developments, greener oxidants, including molecular oxygen[46, 47] and even air,[34, 48] have been found to be effective for the re-oxidation of Pd(0), thus, avoiding the production of stoichiometric metal salts and toxic hydroquinone by-products.

Jung and co-workers have carried out extensive research into the oxidative Heck reaction. In 2003, they were the first to demonstrate the use of molecular oxygen as a cheap, and non-toxic oxidant for the oxidative Heck reaction (Scheme 1.8).[46] A range of olefins **1.7** and electron-withdrawing and -donating aryl boronic acids **1.11** were successfully coupling in good *E*-selectivity and yields (**1.8**, 52-92%). The use of an aryl boronic ester **1.14** was found to reduce the amount of side product formation (homo-coupling and the corresponding phenol), when compared to the corresponding boronic acid **1.11**.



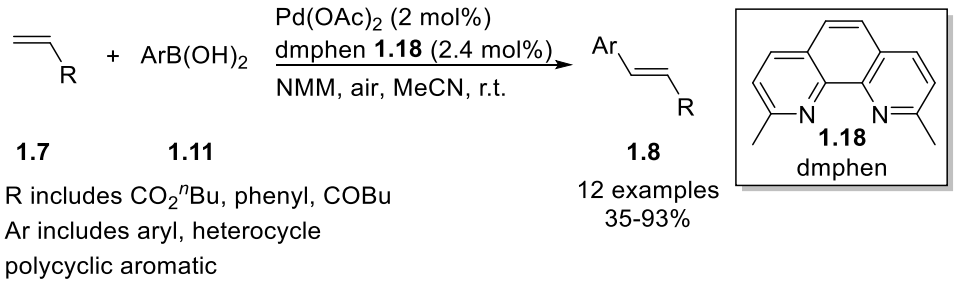
Scheme 1.8: First oxidative Heck coupling reaction with molecular oxygen as an oxidant[46]

In 2004, Jung and co-workers built on their initial work by coupling alkenylboron species **1.15** or **1.16** utilising milder conditions than their previous study (23 °C vs, 50 °C).[49] These conditions furnished coupled diene products **1.17** with good selectivity and high yields (76-90%) (Scheme 1.9). Furthermore, the alkene stereochemistry of the alkenylboron species **1.15** or **1.16** was also retained during the coupling reaction.



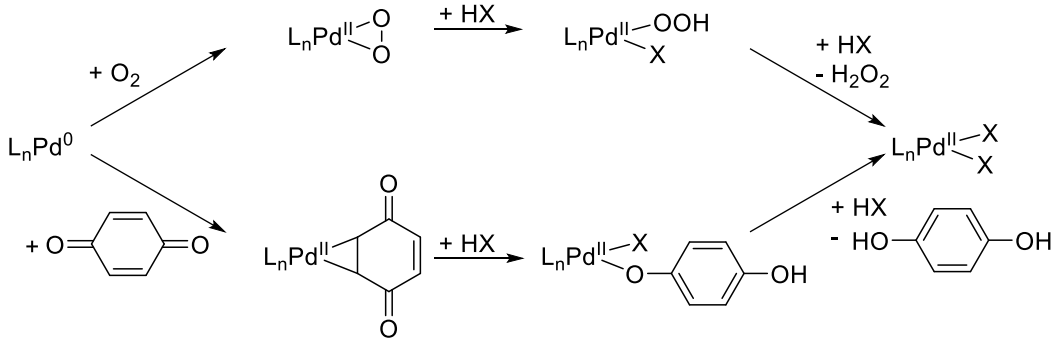
Scheme 1.9: Oxidative Heck coupling reactions under Jung's milder conditions[49]

In 2006 Larhed *et al.* demonstrated that a ligand modulated reaction could aid in the re-oxidation of the catalyst to the extent that O_2 in air (*ca* 20% O_2) is sufficient for catalytic turnover, thereby improving the safety and applicability of the reaction.[34] They demonstrated that $Pd(OAc)_2$ (2 mol%), 2,9-dimethyl-1,10-phenanthroline (dmphen) **1.18** (2.4 mol%) and *N*-methylmorpholine (NMM) at room temperature could successfully furnish the desired Heck-type product **1.8** (34-94%) (Scheme 1.10). A scale up to 50 mmol was safely carried in an open-air vessel.



Scheme 1.10: Oxidative Heck reaction carried out with air as oxidant[34]

These important initial reports, especially by Jung *et al.*, laid the foundations for molecular oxygen to be a common and green oxidant for oxidative Heck chemistry. Interestingly, the mechanism for re-oxidation of Pd(0) by molecular oxygen and *p*-benzoquinone proposed by Stahl *et al.* are mechanistically similar (Scheme 1.11).[45]



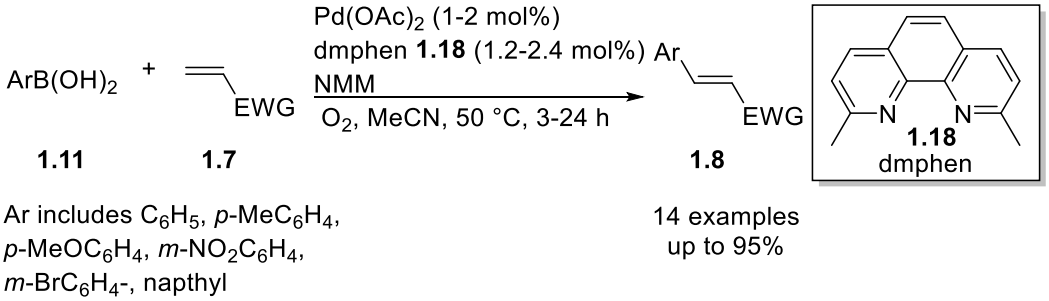
Scheme 1.11: Mechanism for the re-oxidation of Pd(0) to Pd(II)[45]

1.2.4 Ligand Modulated Oxidative Heck Reaction

More recently, ligand-modulated Pd(II)-catalysed oxidative Heck reactions have become common practice.[31, 40] In the absence of ligands, palladium(0) species can aggregate in clusters of unreactive palladium (palladium black), which can impede coupling.[30] Ligands can not only stabilise the active palladium species and hinder the formation of the unreactive aggregates, but can also render enantioselective transformations possible through the employment of chiral ligands.[39] Several types of ligands have been employed in oxidative Heck couplings such as phosphines,[29, 32, 50] *N*-

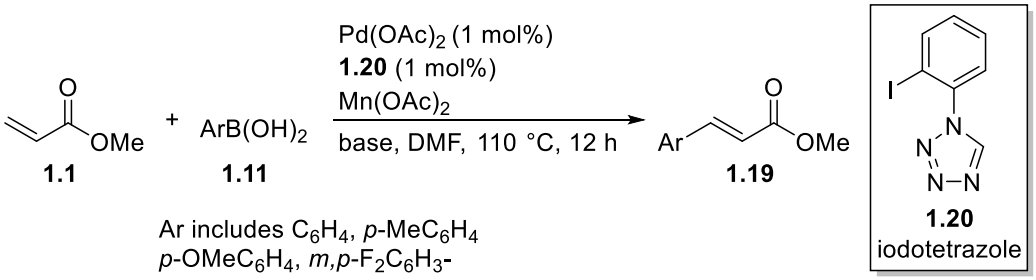
heterocyclic carbenes,[51] sulfoxides[52, 53] and bidentate nitrogen (*N*,*N*-type) ligands.[34, 47, 54] The bidentate (*N*,*N*-type) ligands are particularly popular as they can facilitate the re-oxidation of palladium(0) with molecular oxygen. They are also cheap, often commercially available or easily synthesised, and have a high air and moisture stability in comparison with phosphine ligands.[31] However, both nitrogen-based and phosphine ligands have been employed in oxidative Heck reactions in recent years.[31, 39, 40]

Larhed and co-workers were the first to disclose a ligand modulated oxidative Heck reaction in 2004.[47] They demonstrated that dmphen **1.18** can be used to stabilise the palladium(II) catalyst, avoid aggregation of palladium black and aid in re-oxidation to Pd(II). They reported that $Pd(OAc)_2$ (1 – 2 mol%), dmphen **1.18** (1.2-2.4 mol%), and *N*-methylmorpholine (NMM) base in acetonitrile could be used to couple various aryl boronic acids **1.11** with electron-withdrawing alkenes **1.7** (Scheme 1.12). Pleasingly, upon the addition of **1.18** as ligand, catalyst loadings could be reduced from 10 mol% to 1 mol%. Yields were good to excellent for electron rich boronic acids (70-95%), moderate to good for electron-withdrawing *meta*-substituted aryl boronic acids (40-77%), and unfortunately, *para*-substituted electron-withdrawing aryl boronic acids were not reactive.



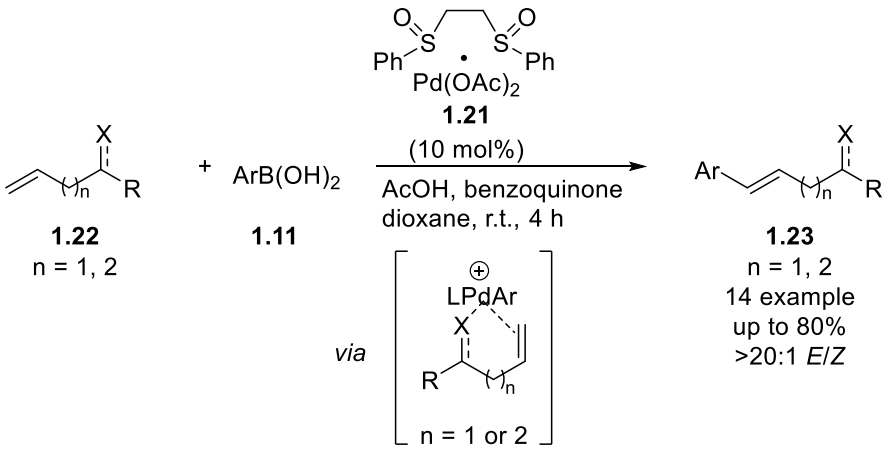
Scheme 1.12: First reported ligand modulated oxidative Heck reaction with dmphen **1.18**[47]

In 2004, Oh and co-workers developed an iodotetrazole ligand **1.20** for use in Heck-type coupling reactions.[55] Although the focus of the publication was a Heck reaction between aryl iodides and acrylates, they also investigated the coupling of aryl boronic acids **1.11** and methyl acrylate **1.1** with $Pd(OAc)_2$ (1 mol%), **1.20** (1 mol%) and additive $Mn(OAc)_2$ (Scheme 1.13). Reaction conditions were comparatively harsh for an oxidative Heck reaction (110 °C, base, DMF, 12 h), however, the conditions were relatively successful, achieving yields of 75% of **1.19**.



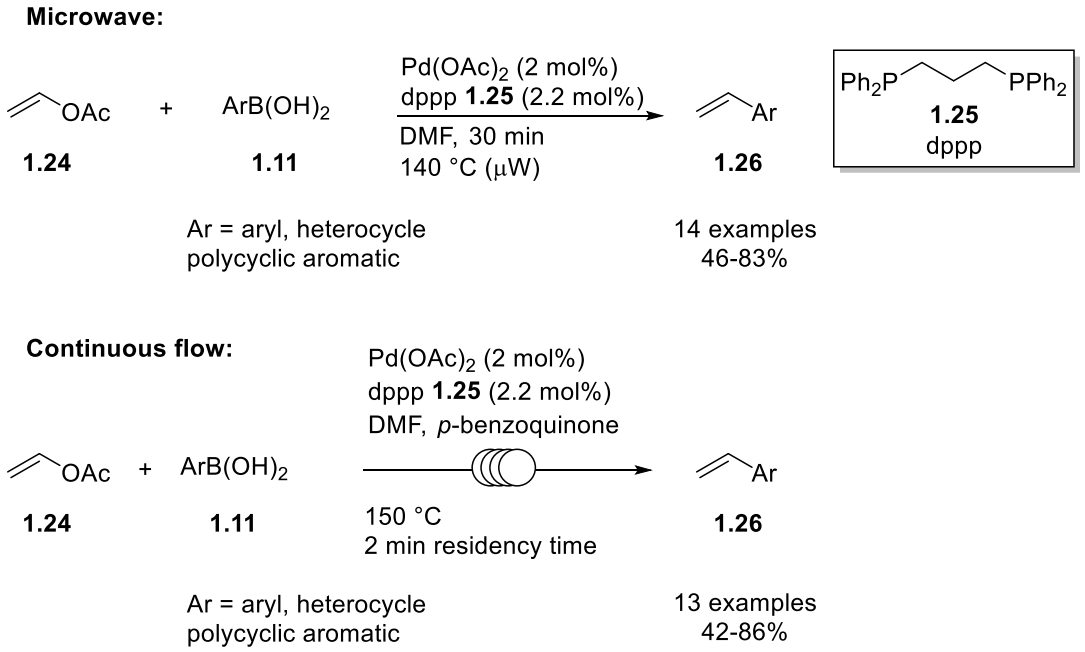
Scheme 1.13: Iodotetrazole ligand **1.20** in oxidative Heck reactions[55]

The White group investigated the use of Pd(II)/sulfoxide catalyst **1.21** within a chelation controlled oxidative Heck reaction with excellent *E*/*Z*-ratio and selectivity.[52] They suggest that arylated Pd(II)/sulfoxide intermediate chelates through the alkene and the oxygen or nitrogen functionality of **1.22** to form a chelation cycle to allow for selective arylation of the terminal position of the alkene over the internal position (Scheme 1.14). Olefin substrates **1.22**, where 5- to 6-membered chelation cycles could form, reacted the most selectively with a range of aryl boronic acids **1.11**. Minor modifications (slightly elevated temperature and reaction time) allowed this chelation control protocol to be applied to the coupling of vinylic pinacol boronic esters with alkenes in good yields and excellent *E*,*E*-diene and polyene selectivity.[53]



Scheme 1.14: Chelation control oxidative Heck reported by White *et al*.[52]

Despite the advantages of using nitrogen based ligands for oxidative Heck reactions due to the susceptibility of phosphine ligands to oxidation,[56] oxidative Heck coupling reactions involving phosphine ligands are known.[29, 32, 50, 57-59] Larhed and co-workers utilised bidentate phosphine ligand **1.25** to synthesise styrenes *via* the vinylation of boronic acids **1.11** with vinyl acetate **1.24** under microwave irradiation (Scheme 1.15).[59] Liberation of styrene product **1.26** from the catalytic cycle by β-acetate elimination, negated the need for base and oxidant as the active species remains isohypsic at Pd(II). An inert atmosphere was not required despite the use of phosphine ligand **1.25**. In addition, this reaction was tailored to continuous flow chemistry in a later publication (Scheme 1.15).[57] Larhed and co-workers found dppp ligand **1.25** was vital for the stability of the Pd(II) catalyst under flow chemistry conditions. Pleasingly, yields were comparable between continuous flow[57] and with microwave irradiation,[59] improving the reaction time significantly. Furthermore, continuous flow allowed for the reaction to be scaled up to 10 mmol with no detriment to yield (1 mmol 80% vs. 10 mmol 77%).

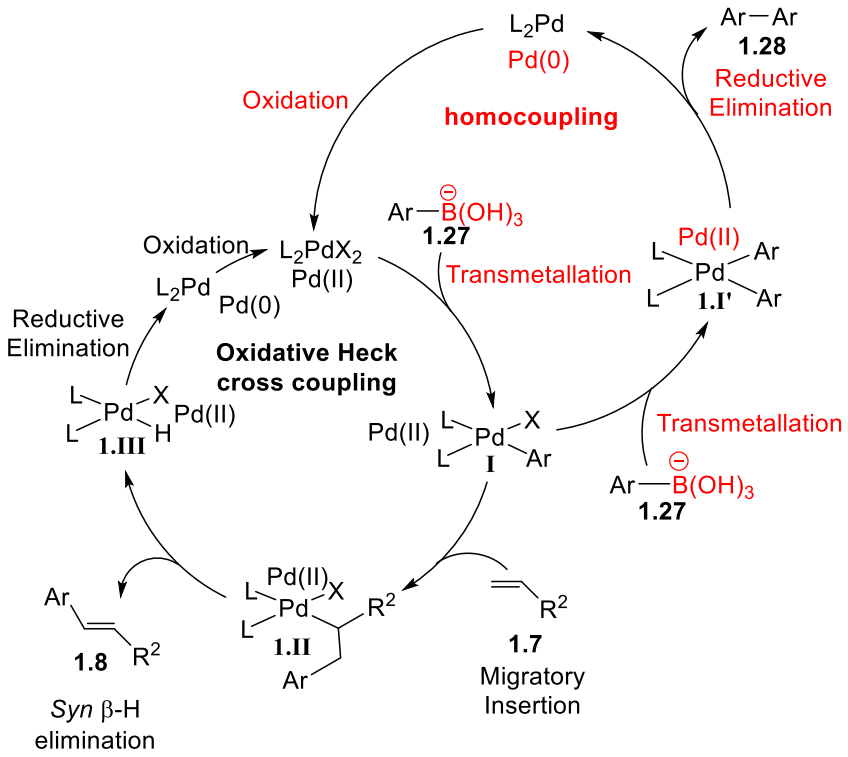


Scheme 1.15: Use of bidentate phosphine ligand in an oxidative Heck coupling reaction with microwave irradiation and in continuous flow[57, 59]

1.2.5 Base-Free Oxidative Heck Reactions

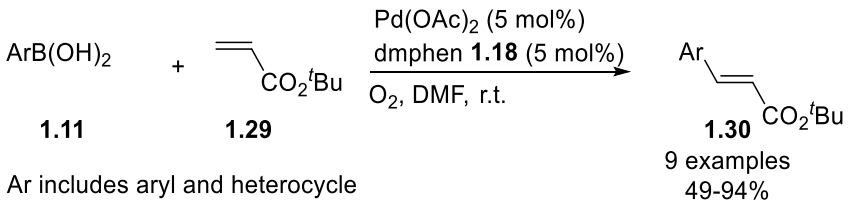
Palladium-catalysed cross-coupling reactions with organoboron species are known to be accelerated in the presence of base, as it aids in the transmetallation of the species *via* organoborate salts **1.27**.[ii] Unfortunately, organoborate salts **1.27** themselves are very reactive, resulting in undesired side product formation, mainly homocoupling **1.28** albeit in low yields (Scheme 1.16).[31] Jung and Larhed have led the way in furthering the developments in palladium(II)-catalysed oxidative Heck reactions by investigating base-free catalytic systems.

[ii] Under homogenous biphasic reaction conditions, it is thought that the addition of base activates the palladium catalyst to form an oxo-palladium species. However, in homogeneous monophasic reaction conditions, as is the case for most oxidative Heck reactions, it is thought that base activates the boron coupling species in the formation of a boronate species.[34]



Scheme 1.16: The role of base within the oxidative Heck cycle and side product formation

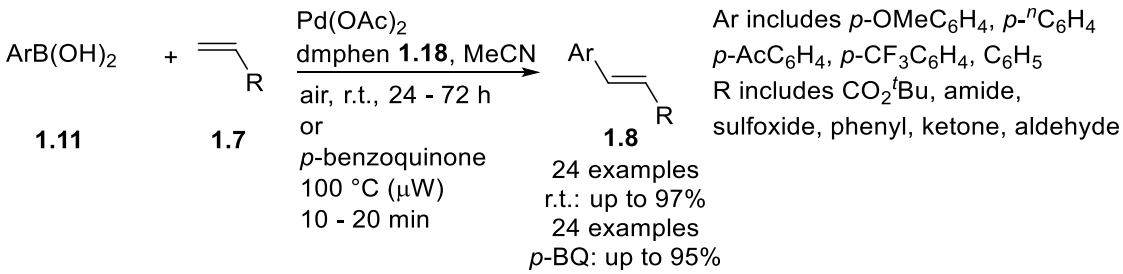
In 2006, Jung and co-workers demonstrated the first base-free oxidative Heck reaction (Scheme 1.17).[30] Various olefins, including *tert*-butyl acrylate **1.29** and aryl boronic acids **1.11** were coupled together to furnish **1.30** in moderate to excellent yields (49-94%, Scheme 1.17). Side product formation associated with reactive borate salts was successfully avoided through this mild, base-free preparation.



Scheme 1.17: Base-free oxidative Heck conditions published by Jung *et al.*[30]

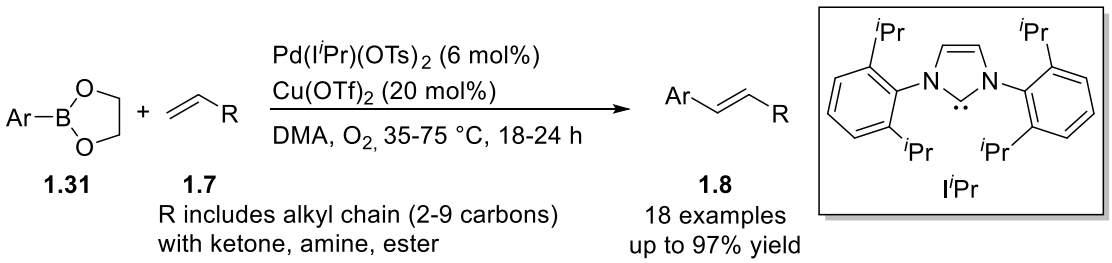
The Larhed group also developed a base-free oxidative Heck protocol, studying the reaction in both batch and under microwave irradiation (Scheme 1.18).[48] The group

employed optimised conditions of $Pd(OAc)_2$ (2 mol%), dmphen **1.18** (2.4 mol%) in MeCN and employed either air as an oxidant (open vessel, 24-27 h, r.t.) or *p*-benzoquinone (sealed microwave tube, 100 °C, 10 min). Both reaction conditions gave comparable results in moderate to excellent yield for a wide variety of olefin substrates **1.7** and aryl boronic acids **1.11**.



Scheme 1.18: Base-free oxidative Heck coupling employing air or *p*-benzoquinone as oxidant[48]

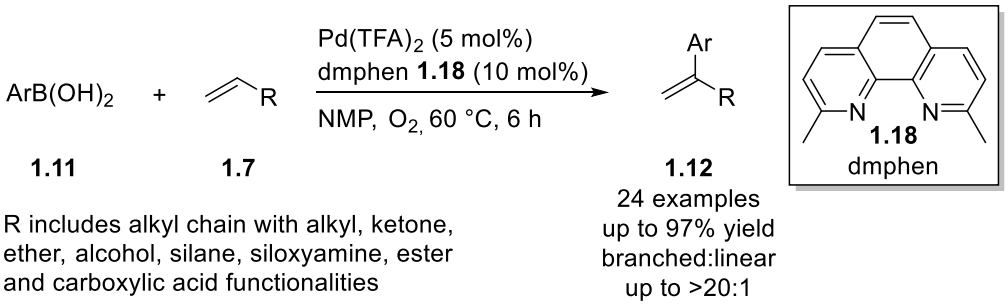
1n 2010, Sigman and Werner reported a mild, base-free oxidative Heck protocol for the coupling of aryl boronic esters **1.31** with electronically unbiased olefins **1.7** (Scheme 1.19).[51] High selectivities were achieved for *E*-styrenyl products **1.8** from olefins **1.7**, with functionality located at various chain lengths (2-9 carbons) away from the alkene reaction site.



Scheme 1.19: Sigman's base-free oxidative Heck protocol with electronically unbiased olefins **1.7**[51]

Stahl and co-workers also disclosed a base-free oxidative Heck protocol with electronically unbiased olefins **1.7** and aryl boronic acids **1.11** (Scheme 1.20).[54]

However, in this instance, branched alkenes **1.12** were achieved in generally very good selectivity from the corresponding mono-substituted alkene **1.7** with various functionalities remote from the reaction site. The group postulate that the origin of the selectivity for the branched product **1.12** results from the avoidance of steric clash with the methyl groups of dmphen **1.18.**



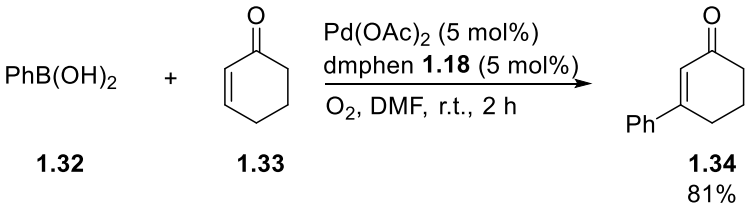
Scheme 1.20: Oxidative Heck reaction to selectively form branched alkene **1.18**

1.2.6 Oxidative Heck Reactions with Cyclic Alkenes

Traditionally, cyclic alkenes and enones have been considered challenging substrates for Pd(0)-catalysed Heck-type reactions, often with harsh reaction conditions required.[25, 30 60] Typically, this is because the reaction is in competition with conjugate addition, resulting primarily from the cyclic substrate being stereochemically precluded from undergoing *syn* β-hydride elimination to furnish the Heck-type product.[61, 62] Pleasingly, the Pd(II)-catalysed oxidative Heck reaction has emerged as a promising alternative for achieving Heck-type coupling with cyclic alkene systems under milder conditions. Despite this, publications of oxidative Heck boron reactions with cyclic alkenes are still uncommon in the literature.

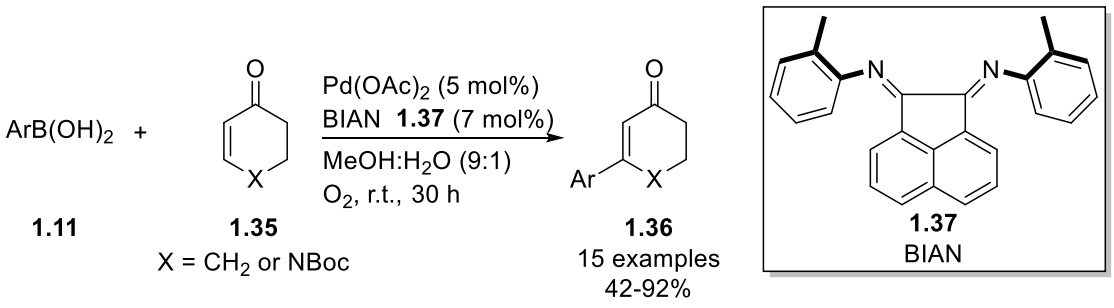
Within their 2006 study investigating base-free oxidative Heck reactions, Jung and co-workers reported a successful coupling reaction with a cyclic enone (Scheme 1.21).[30] Phenylboronic acid **1.32** with cyclohexenone **1.33** successfully furnished the Heck-type

product **1.34** in very good yield (81%). Jung *et al.* suggested that a base is necessary to facilitate *syn* *β*-hydride elimination to generate the Heck-type product and further postulated that *N*,*N*-type ligand dmphen **1.18** is functioning as the base in this circumstance. However, no mechanistic studies were carried out to this effect.



Scheme 1.21: Base-free coupling of phenyl boronic acid with a cyclic enone[30]

Minnaard *et al.* also investigated oxidative Heck reactions on cyclic and acyclic enones,[63] utilising $Pd(OAc)_2$ with *bis*(imino)acenaphthene **1.37** (BIAN) as the ligand (Scheme 1.22). The aryl boronic acid **1.11** scope was more substantial than that of Jung's,[30] achieving moderate to excellent yields of **1.36** (X = CH_2, 42-92%). Furthermore, they successfully carried out a small cyclic enone **1.35** scope, including Boc-protected 2,3-dihydropyridin-4(1*H*)-one (X = NBoc) (74%).

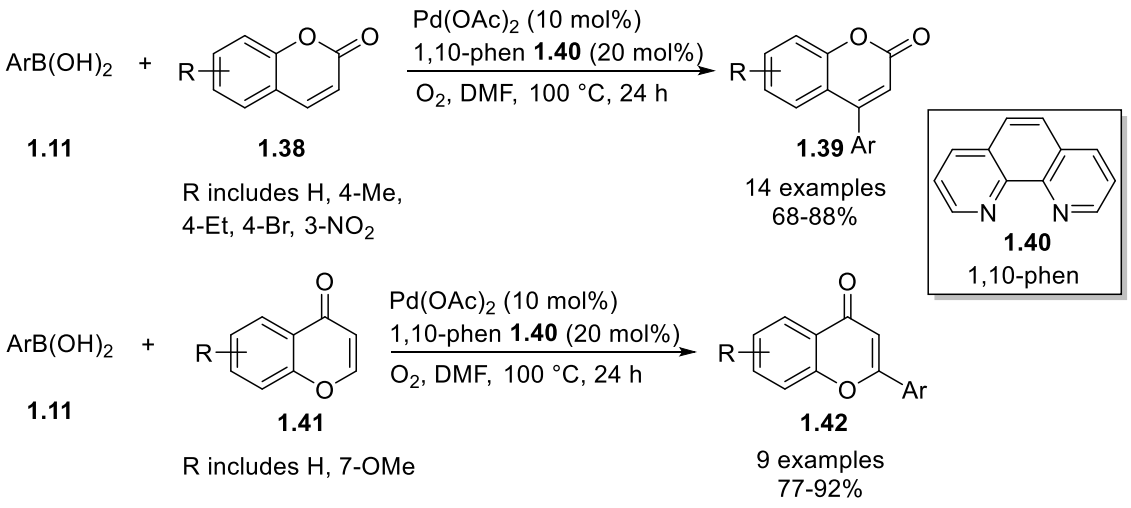


Scheme 1.22: BIAN ligand mediated base-free oxidative Heck reactions cyclic substrate **1.35**[63]

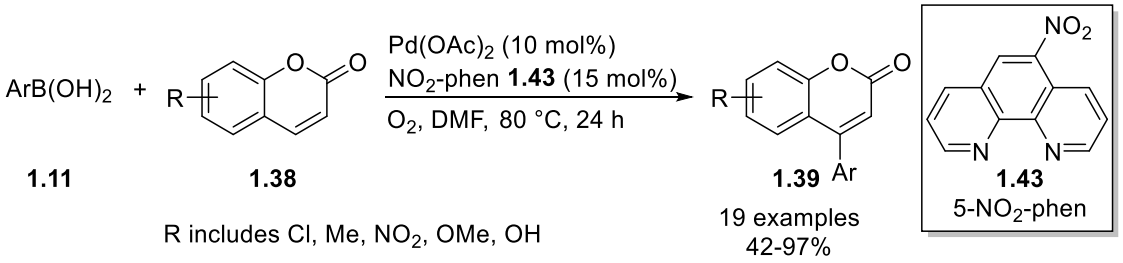
The coupling of coumarins **1.38** with aryl boronic acids **1.11** was reported by two separate groups in 2012: Shafiee[64] (Scheme 1.23) and Duan (Scheme 1.24).[65] Shafiee *et al.* demonstrated the coupling using base-free conditions and 1,10-phenanthroline

1.40 (1,10-phen) as ligand to furnish the coupled coumarin product **1.39** in good yields (68-88%, Scheme 1.23).[64] Furthermore, Sharifee and co-workers also carried out a smaller scope employing substituted chromones **1.41** and aryl boronic acids **1.11** with 1,10-phen **1.40** as ligand to furnish the Heck-type product **1.42** in very good yields (77-92%, Scheme 1.23).[64]

Meanwhile, Duan *et al.* utilised 5-NO_2-1,10-phenanthroline **1.43** (5-NO_2-phen) as ligand with their oxidative Heck coupling of coumarins **1.38** with a range of aryl boronic acids **1.11** (Scheme 1.24).[65] Under optimised conditions, the group successfully carried out a wider coumarin scope than that of Sharifee's,[64] achieving moderate to excellent yields of **1.39** (42-97%).[65]

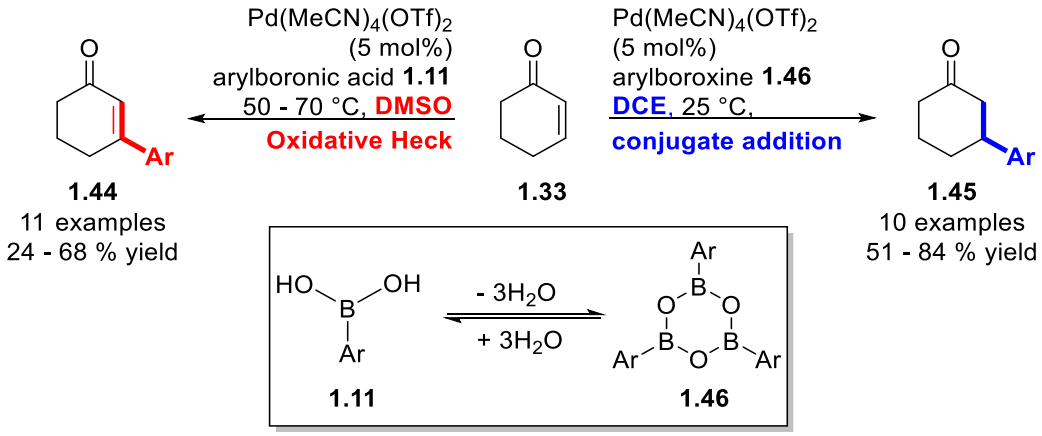


Scheme 1.23: Sharfiee *et al*. conditions for coupling coumarins **1.38** and chromones **1.41** with aryl boronic acids **1.11**[64]



Scheme 1.24: Duan's conditions for coupling coumarins **1.38**[65]

In 2013, the Lee group established an efficient protocol to control the synthesis of the Heck-type product **1.44** or the conjugate addition product **1.45**, simply by switching the solvent in a base- and ligand-free palladium(II)-catalysed reaction (Scheme 1.25).[66] It was determined that a non-polar, aprotic solvent such as dichloroethane (DCE) was required to promote the conjugate addition reaction; whereas a polar, aprotic solvent such as dimethylsulfoxide (DMSO) resulted in the selective formation of the Heck-type product (Scheme 1.25). The group suggested that under base-free and ligand-free conditions, a polar, aprotic solvent is required to facilitate *syn* β-hydride elimination, which in turn allows for the selective switching to oxidative Heck.



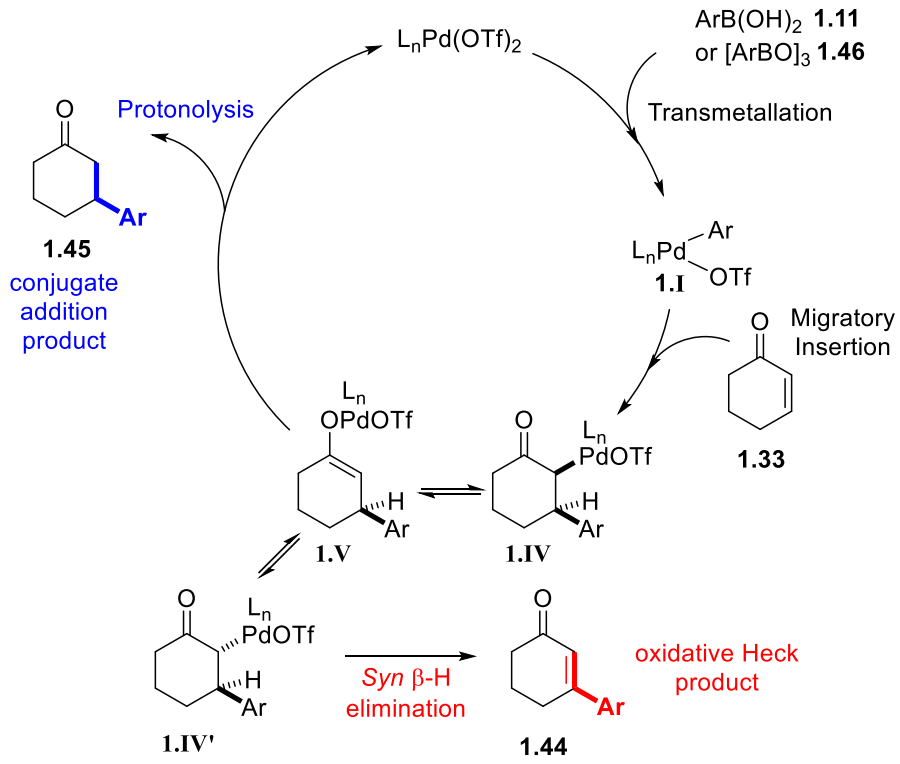
Scheme 1.25: Aryl boron species scope of Lee *et al.*'s selective oxidative Heck and conjugate addition reaction[66]

A range of cyclic enones were subjected to optimised oxidative Heck and conjugate addition reaction conditions to furnish moderate to excellent yields of the desired products (conjugate addition: 51-94%; oxidative Heck: 24-84%). The arylboron reagent substrate scope studies provided some interesting results (Scheme 1.25). It revealed that the conjugate addition reaction required *arylboroxines* **1.46** (the dehydrated trimer of

the corresponding boronic acid, Scheme 1.25)[iii] to perform better.[67] On the other hand, the oxidative Heck reaction gave more positive results when aryl boronic acids **1.11** were employed as coupling partners. In both reactions *o*-, *m*- and *p*-substituted arylboron compounds and electron-withdrawing and -donating substituents are tolerated in each case.

Lee *et al.* suggested that the mechanism for the formation of the oxidative Heck and the conjugate addition product diverges after the migratory insertion step (Scheme 1.26).[66] It is theorised that intermediate **1.IV** cannot undergo *syn* β-hydride elimination, but epimerisation to intermediate **1.IV′** places the β-H in the correct position for *syn* β-hydride elimination to occur, resulting in the oxidative Heck product **1.44**. Alternatively, protonolysis through intermediate **1.V** or **1.IV** can produce the conjugate addition product **1.45**. To selectively synthesise the oxidative Heck product, the *syn* β-hydride elimination must be facilitated. The group hypothesise that polar, aprotic solvents such as DMSO must have a role in this, potentially helping to stabilise the cationic palladium centre and also facilitating the epimerisation of **1.IV** to **1.IV′**.[66]

[iii] Commercially available "boronic acids" exist as an equilibrium mixture of the boronic acid **1.11** and the boroxine **1.46**, the trimer of the corresponding aryl boronic acid. To be certain of which boron species is being used the commercial equilibrium mixture must either be recrystallised with water to the boronic acid **1.11** or dehydrated under vacuum *via* heat to the boroxine **1.46**.[67]



Scheme 1.26: Proposed mechanism for the formation of conjugate addition **1.45** and oxidative Heck **1.44** products[66]

1.3 Enantioselective Oxidative Heck Reaction

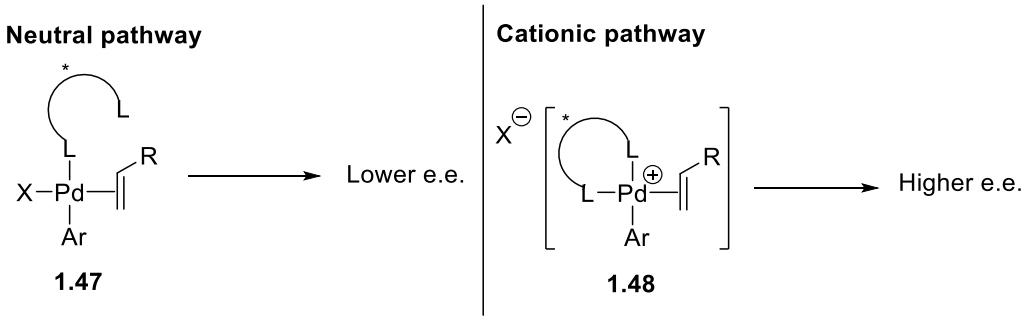
1.3.1 Introduction

Asymmetric palladium(0)-catalysed Heck couplings were one of the first catalytic asymmetric carbon-carbon bond forming reactions to be studied, with the *intra*molecular Heck reaction successfully applied to natural product synthesis[68] and to the construction of quaternary centres.[69] The first reports of asymmetric intramolecular Heck reactions were independently investigated by Overman[70] and Shibasaki[71] in 1989. However, the *inter*molecular Heck coupling reaction has proven to be more challenging, especially for acyclic systems.[39, iv] Uemura and co-workers first reported an asymmetric

[iv] There are several privileged cyclic alkene systems which can successfully undergo intermolecular Pd(0)-catalysed Heck reactions, where the *syn β*-H elimination occurs at the β' position.[39] For examples of this type of *syn β*-H elimination under Pd(II)-catalysis please refer to Schemes 1.28 – 1.30.

intermolecular Pd(0)-catalysed Heck coupling with an acyclic prochiral alkene with only 17% enantiomeric excess.[72]

Through the development of palladium(II) catalysis, significant advances have been demonstrated in both acyclic and cyclic asymmetric coupling reactions. The oxidative Heck reaction has been shown to exhibit excellent enantiomeric ratios and yields, along with often being performed under mild conditions.[28, 31] The focus of this review will be the advances in Pd(II)-catalysed asymmetric *inter*molecular oxidative Heck catalysis. It has been suggested that Pd(II)-catalysis is more likely to proceed through the cationic pathway **1.48**, rather than the neutral pathway **1.47**. The chiral bidentate ligand is therefore more likely to be fully bound to the catalyst, resulting in higher enantiomeric ratios (Scheme 1.27).[39, 58]



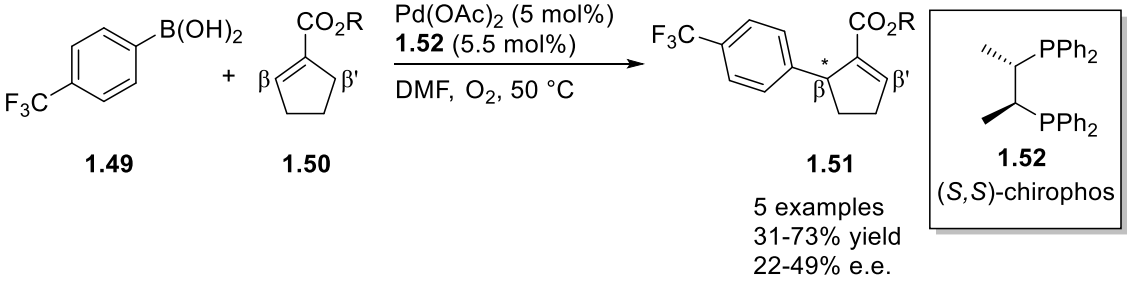
Scheme 1.27: Neutral and cationic pathways in oxidative Heck and their significance in e.e.[58]

1.3.2 Cyclic Alkenes

1.3.2.1 Enantioselective oxidative Heck reactions

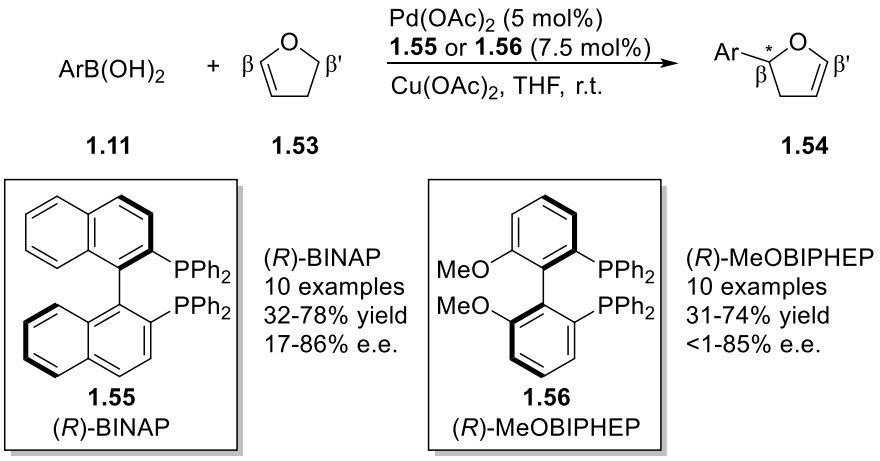
In 2005, Mikami and co-workers published the first catalytic asymmetric oxidative Heck reaction (Scheme 1.28).[29] A screen of various chiral ligands was carried out with (*S*,*S*)-chiraphos **1.52** being identified as the optimal. A range of pro-chiral cyclopentane-1-carboxylates **1.50** were successfully coupled with electron-withdrawing boronic acid **1.49** in moderate to good yield (31-73%) and modest e.e.s (22-49%). However, the

reaction itself and the potential it offered was pioneering. It is worth highlighting that enantioselective oxidative Heck reactions are possible with substrates such as **1.50** because the *syn* β-H elimination occurs at the β'-position instead of the β-position to deliver a stereogenic centre in compounds **1.51** (Scheme 1.28).



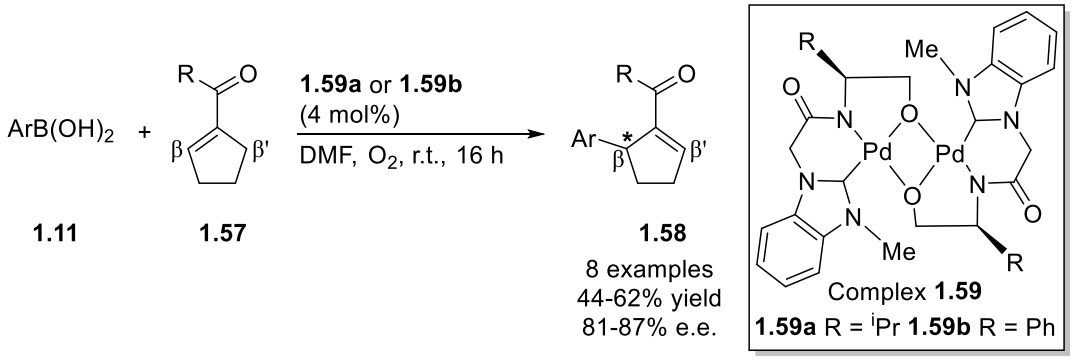
Scheme 1.28: First enantioselective oxidative Heck reaction[29]

Gelman and co-workers reported an enantioselective oxidative Heck protocol for 2,3-dihydrofuran **1.53** with chiral phosphine ligands (*R*)-BINAP **1.55** or (*R*)-MeOBiphep **1.56** (Scheme 1.29).[58] Electron-withdrawing and electron-donating aryl boronic acids **1.11**, with the exception of *o*-substituted boronic acids, provided moderate to good e.e.s (42-86%) and yields (31-78%).



Scheme 1.29: Enantioselective reaction with 2,3-dihydrofuran with chiral phosphine ligands **1.55** and **1.56**[58]

Jung and co-workers further contributed to the development of the oxidative Heck reaction, in this instance building on the original work by Mikami *et al.,* with the enantioselective coupling of cyclopentenes **1.57** and aryl boronic acids **1.11**.[73] Favouring a tridentate NHC-amidate-alkoxide palladium(II) complex **1.59**, Jung and co-workers considerably improved upon the e.e.s (81-87%) reported by Mikami *et al.*[29] (Scheme 1.30 *vs.* 1.28) and the boronic acid **1.11** scope, producing moderate to good yields of **1.58** (44-62%).

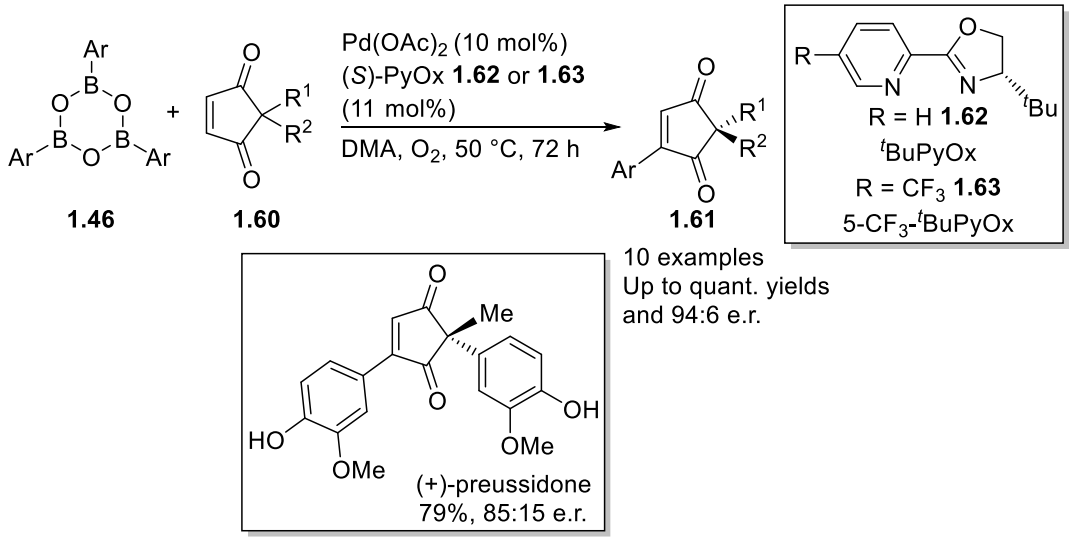


Scheme 1.30: Jung and co-workers complexes **1.59** achieving higher enantioselectivities than previously reported[73]

1.3.2.2 Oxidative Heck desymmetrisation reactions on 2,2-disubstituted cyclopentene-1,3-diones

In 2015, the Lee group reported the first oxidative Heck desymmetrisation reaction in literature, focusing on 2,2-disubstituted cyclopentene-1,3-diones **1.60** (Scheme 1.31).[74] The oxidative Heck reaction is an ideal candidate in the desymmetrisation of cyclic enedione **1.60** because Pd(II)-catalysis is far more tolerant of cyclic systems than the Pd(0)-catalysed Heck reaction[61] (see Section 1.2.6). Furthermore, desymmetrisation reactions are particularly useful as they move the steric burden away from the enantioselective reactive centre driving the formation of all-carbon quaternary centres, which are typically very challenging to form enantioselectively.[75, 76]

The group employed chiral (*S*)-PyOx ligands **1.62** or **1.63** with $Pd(OAc)_2$ in an atmosphere of molecular oxygen to successfully furnish the desymmetrised product **1.61** in up to quantitative yields and up to 94:6 e.r.. Through the racemic reaction study, the reaction proved itself to be very tolerant of many functionalities, including those sensitive to oxidation. Furthermore, the efficient synthesis of (+)-preussidone was demonstrated in one step from **1.60** in a yield of 79%, and 85:15 e.r. (Scheme 1.31).



Scheme 1.31: Oxidative Heck desymmetrisation reaction with 2,2-disubstituted cyclopentenediones **1.60**[74]

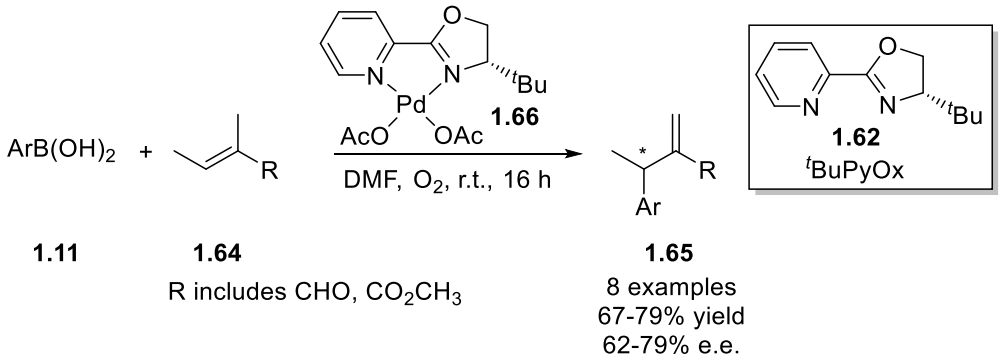
1.3.3 Acyclic Alkenes

1.3.3.1 Enantioselective oxidative Heck reactions

The intermolecular asymmetric Heck-type coupling of acyclic alkenes has traditionally been considered challenging, as discussed above in Section 1.3.1. Consequently, the successful application of palladium(II) catalysis to the intermolecular coupling of acyclic alkenes with aryl boronic acids by Jung and co-workers is considered to be pioneering work.[33]

Within their 2007 study, Jung and co-workers opted to use (*S*)-PyOx ligands. ^{t}BuPyOx **1.62** was successfully applied as the ligand with $Pd(OAc)_2$ as the catalyst to

enantioselectively couple a range of boronic acids **1.11** with alkene **1.64** (Scheme 1.32).[33] Enantioenriched coupled product **1.65** was furnished in good yields (67-79%) and promising e.e.s (62-75%), considering how challenging these asymmetric transformations typically are. Pre-forming the $Pd(OAc)_2$(^{t}BuPyOx) **1.66** catalyst gave significant improvement on e.e.s compared to pre-mixing $Pd(OAc)_2$ with ^{t}BuPyOx **1.62** prior to the reaction.



Scheme 1.32: First reported asymmetric oxidative Heck reaction with pyridinyloxazoline ligands[33]

Based on the analysis of single crystal x-ray crystallography data of the chiral palladium catalyst, Jung and co-workers suggest that the migratory insertion step of the alkene during the oxidative Heck catalytic cycle (Section 1.2.1, Scheme 1.4) is the key enantiodetermining step (Figure 1.1).[33] The increased steric hindrance of the acyl-group in intermediate **1.VIb** with the *tert*-butyl group in comparison to the methyl group in intermediate **1.VIa**, results in intermediate **1.VIa** being favoured. The preference of intermediate **1.VIa** leads to the observed enantioselectivity.

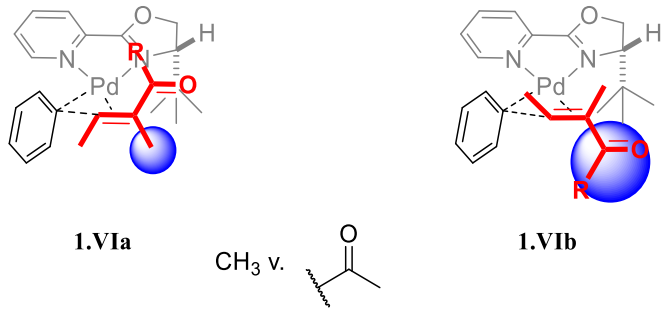


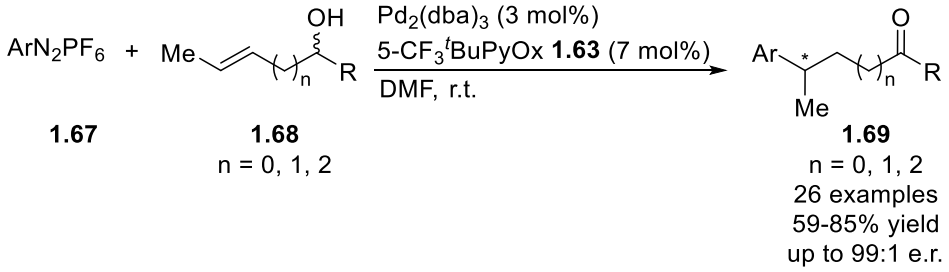
Figure 1.1: Proposed conformations for the enantiodetermining step with Pd(II)/^{t}BuPyOx catalyst [33]

Following on from this work, Jung and co-workers also applied their tridentate NHC-amidate-alkoxide ligand **1.59** previously discussed in Section 1.3.2 (Scheme 1.30) to the asymmetric coupling of acyclic alkenes **1.7** with aryl boronic acids **1.11.** The e.e.s reported are very good (82-92% e.e.) whilst the yields are a little modest (29-61%). It is thought that this tighter binding ligand, although excellent for enantioselectivity, does reduce the reactivity of the catalyst and thus effects the yield. The group also noted an increase in the amount of oxidative deborylation and phenolic side products.[73] Nonetheless, the enantioselectivities achieved by Jung *et al.* were unparalleled at the time of publication.

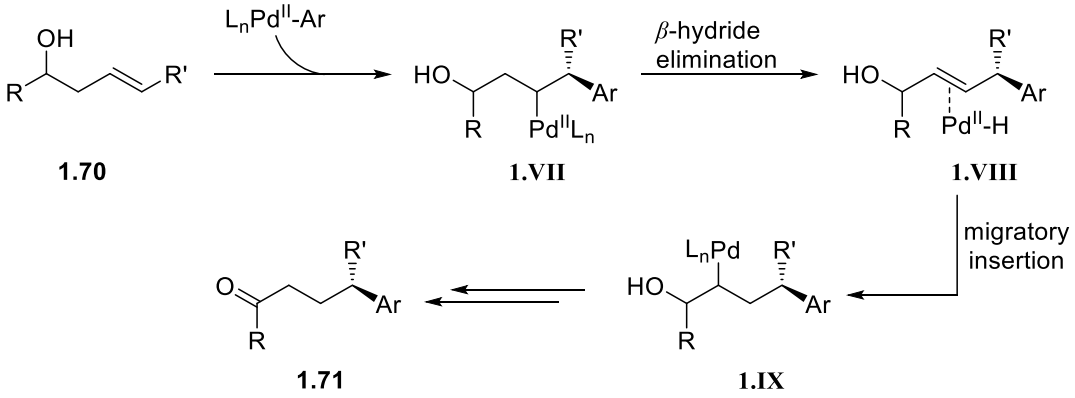
1.3.3.2 Enantioselective redox-relay oxidative Heck reaction

A more recent development in enantioselective intermolecular oxidative Heck reactions is redox-relay catalysis. Developed by Sigman and co-workers, the concept of redox-relay catalysis was first reported in 2012 as a Heck-Matsuda coupling of allylic alcohols **1.68** with aryldiazonium salts **1.67** to furnish chiral carbonyl products **1.69** with good yields and excellent e.r.s (Scheme 1.33).[77] Subsequently, investigations have been directed towards the development of a Pd(II)-catalysed oxidative Heck redox-relay reaction, to expand the scope and utility of the reaction.[36, 78-81] This work is particularly interesting and remarkable because not only does it allow for the installation of remote

stereogenic centres but it also has excellent site-selectivity and can distinguish between almost identical C–Hs in the *syn* β-hydride elimination steps (Scheme 1.34, **1.VII→1.IX)**.



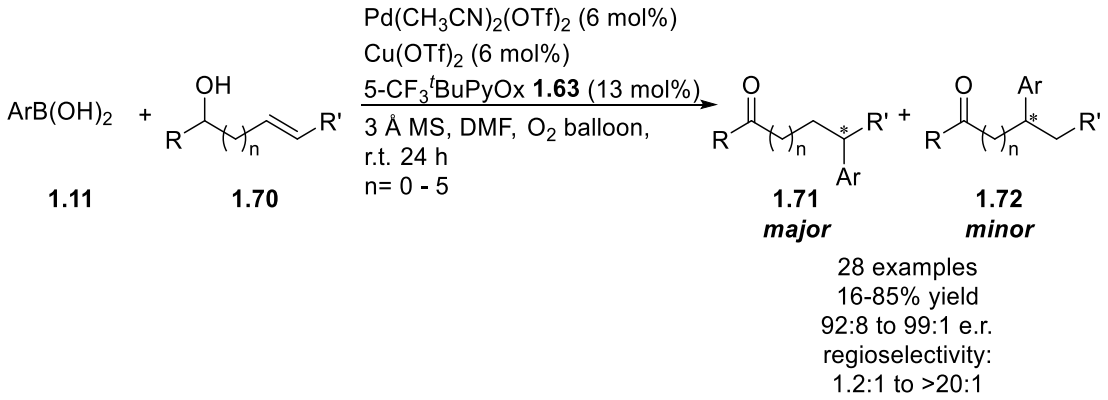
Scheme 1.33: Sigman and co-worker's Heck-Matsuda asymmetric redox-relay reaction[77]



Scheme 1.34: "Chain-walking" mechanism of the redox-relay protocol

In 2013, Sigman reported the first oxidative Heck redox-relay coupling reaction of alkenyl alcohols **1.70** and aryl boronic acids **1.11** (Scheme 1.35).[78] Utilising chiral (*S*)-PyOx ligand **1.63** (13 mol%) and $Pd(CH_3CN)_2(OTs)_2$ (6 mol%) as catalyst, copper(II) triflate (6 mol%) in conjunction with molecular oxygen as oxidant and 3 Å molecular sieves (to avoid retardation of oxidation),[82] redox-relay products **1.71** were successfully furnished in poor to very good yields (16-85%) and even better enantiomeric ratios (up to 99:1 e.r.).

Sigman *et al*. suggested the use of 5-CF_3^{t}BuPyOx **1.63** as ligand renders the palladium catalyst electrophilic enough to promote re-insertion into the chain rather than dissociation. Subsequent migratory insertion and *syn* β-hydride elimination steps sees the palladium catalyst "chain-walk" along the molecule, before tautomerisation of the enol to yield coupled carbonyl product **1.71** (Scheme 1.34). It is noteworthy that the racemic alcohol has no effect on the enantioselection of the reaction, but the stereochemistry of the alkene does. An *E*-alkene results in an *S*-configuration and a *Z*-alkene gives the opposite, an *R*-configuration.[78]



Scheme 1.35: Enantioselective oxidative Heck redox relay reaction[78]

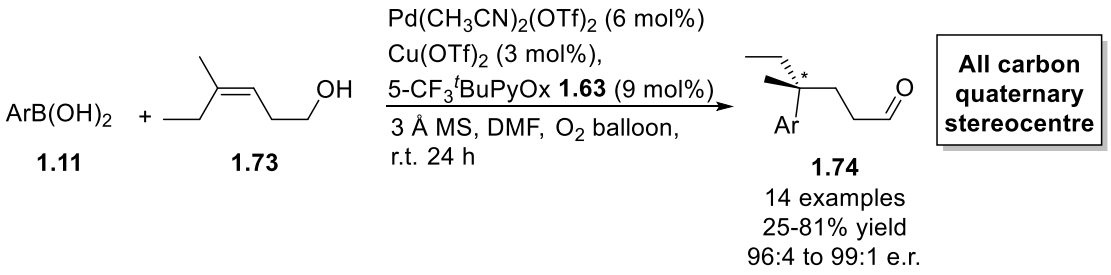
Mechanistic investigations were performed, in order to understand the regioselectivity observed. Along with establishing that the enantioselectivities observed are independent of either coupling partner, the authors also suggest the excellent site selectivity is controlled by the nature of the boronic acids **1.11** used, the chain length and substitution of the alkenyl alcohol substrate **1.70**. A plot of site selectivity ratios *vs.* Hammett σ-values shows a trend in the electronics of the aryl boronic acid **1.11** and the regioselectivity. Electron-withdrawing boronic acids resulted in higher regioselectivities than electron-donating variants. Chain length also proved to have an influence on site selectivity, a plot of selectivity ratio vs ^{13}C NMR chemical shifts of

the alkene (the most down-field C is the furthest from alcohol) also reveals a trend: a decrease in selectivity as chain length is increased, electronics again playing a role in the selectivity of the reaction. Both the major and the minor products exhibit good enantioselectivities, prompting Sigman and co-workers to suggest that the major and minor products arise due to the two different faces of the alkene presenting itself to the chiral catalyst during the migratory insertion step, which is more selective for the more downfield shifted carbon of the alkene. Furthermore, computational studies have been carried out into the site selectivity and mechanism of the reaction.[83]

Expanding on their initial investigations, the redox-relay protocol was subsequently extended to the installation of remote quaternary centres (Scheme 1.36).[36] Employing similar reaction conditions to their previous report, Sigman and co-workers demonstrate very high site selectivity in the coupling of aryl boronic acids **1.11** with tri-substituted alkenyl alcohols **1.73,** irrespective of chain length. This report is somewhat in contrast to what was observed with corresponding di-substituted alkenes **1.70** (Scheme 1.35) which did exhibit chain length dependant selectivity. The redox relay products **1.74** were again furnished in excellent enantiomeric ratios (94.5:5.5 to 99:1 e.r.) which is remarkable given the added challenge of constructing an all-carbon quaternary stereocentre. The reaction is highly selective for the more hindered site of the alkene, which confirms the conclusions that the migratory insertion step is more selective for the more down-field shifted carbon and that electronics play an important role in this reaction.

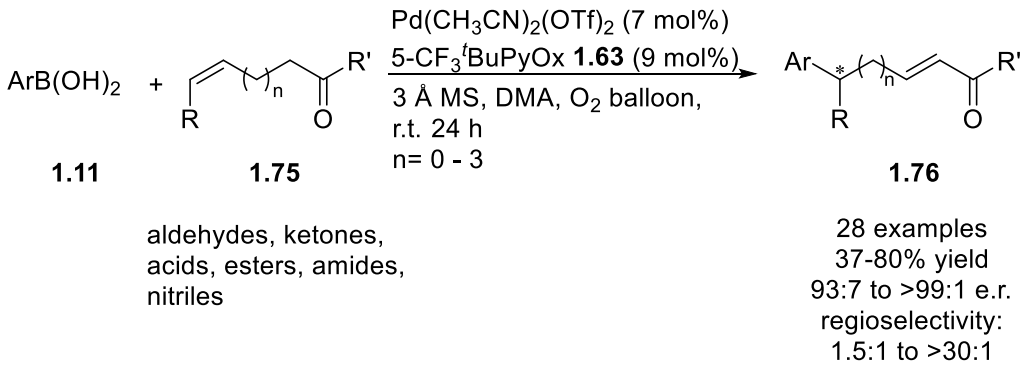
Furthermore, subjecting alkenyl alcohols with pre-existing stereocentres to the reaction results in the preservation of the original stereochemistry, making this a very useful approach for natural product synthesis. This observation suggests that the palladium

species remains ligated on the same face of the molecule through the whole "chain-walking" event (Scheme 1.34).[36]

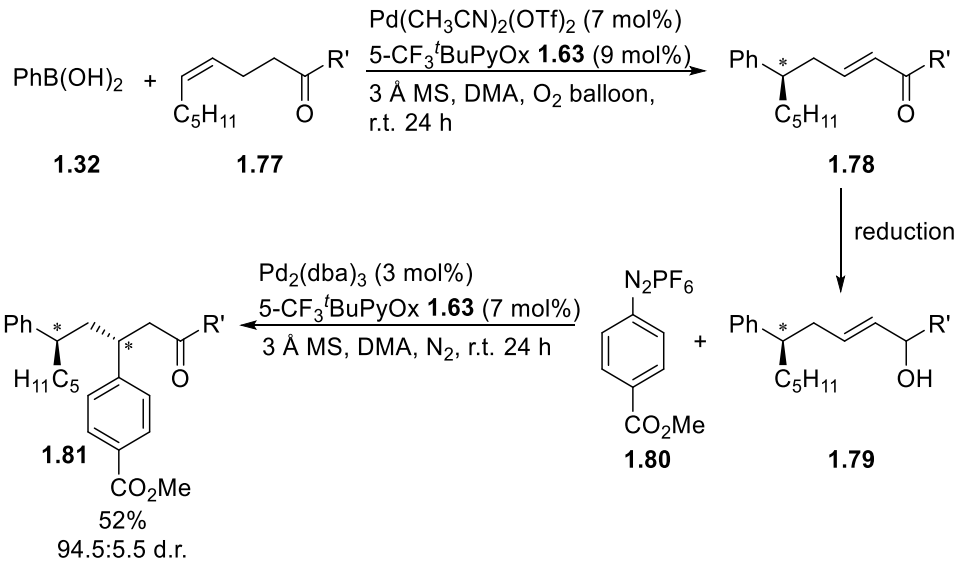


Scheme 1.36: Redox-relay approach to the construction of quaternary stereocentres[36]

In later publications, the group continued to expand the alkenyl scope, investigating alkenyl ketones **1.75** to access coupled α,β-unsaturated ketones **1.76** (Scheme 1.37).[79] In order to get excellent site selectivity with n = 1, the use of DMA as solvent was imperative. The group also developed an iterative Heck-type coupling approach to generate 2 stereocentres in only three synthetic steps (Scheme 1.38). Utilising an oxidative Heck reaction to access enantioenriched **1.78**, a reduction could be performed to furnish the alkenyl alcohol **1.79**, and a subsequent Heck-Matsuda redox-relay reaction could then be invoked to generate **1.81**.



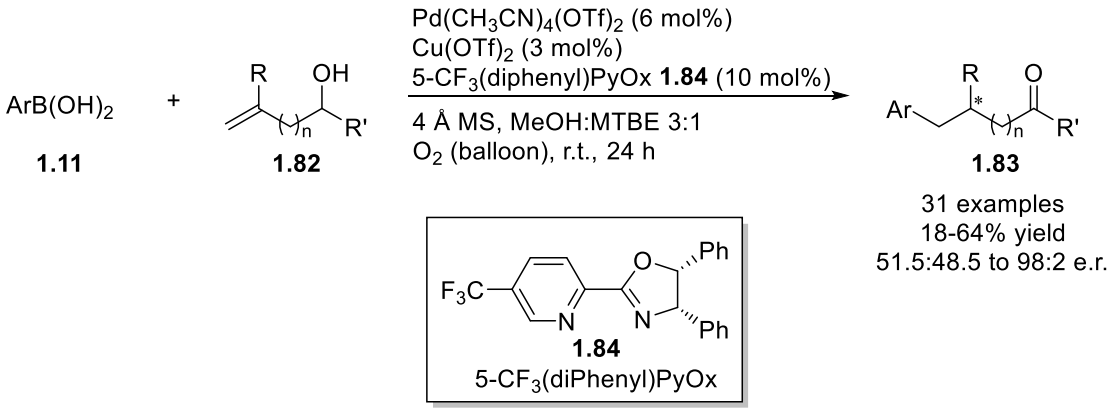
Scheme 1.37: Redox-relay oxidative Heck coupling with α,β-unsaturated ketones



Scheme 1.38: Iterative oxidative Heck redox relay, reduction then Heck redox-relay reaction

1,1-Disubstituted homoallylic alcohols **1.82** were also coupled with aryl boronic acids **1.11** under Pd(II)-catalysed redox-relay conditions (Scheme 1.39).[81] In previous investigations,[36, 78, 79] the new stereocentre is installed at the site of migratory insertion, however, within this study the stereocentre is generated *β* to this position. The challenge here was ensuring the correct *β*-hydride eliminated to yield the redox-relay product over the Heck-type product, which is more thermodynamically stable and has been synthesised under similar reaction conditions in the past.[84] Pleasingly, optimised aerobic redox-relay conditions, and switching to 5-CF_3(diphenyl)PyOx **1.84** as ligand to improve the yield successfully furnish the desired redox-relay carbonyl product **1.83** in poor to good yields (18-64%) and up to excellent enantioselectivities (98:2 e.r., Scheme 1.39). Poor enantioselectivities were achieved when the 1,1-disubstitution on **1.82** was very similar, *i.e.* R = alkyl, presumably due to poor facial differentiation during the enantiodetermining migratory insertion step. Similarly, if the aryl group is not in conjugation with the alkene, *i.e.* R = benzyl, then a lower enantiomeric ratio was also observed. Contrary to the other redox-relay reports discussed above, electron-donating

boronic acids during this study gave better enantiomeric ratios. In previous studies, the chain length had minimal impact on the enantioselectivity of the reaction, however, under these reaction conditions, the enantiomeric ratio decreased with chain length.



Scheme 1.39: Redox-relay catalysis with 1,1-disubstituted allylic alcohols **1.82**

1.4 Pd(II)-Catalysed Conjugate Addition Reaction

1.4.1 Introduction

Conjugate addition (1,4-addition) reactions are a powerful and versatile method for the creation of C–C bonds.[85] The products furnished are often important intermediates en route to the synthesis of complex biologically active molecules, agrochemicals and natural products.[86, 87] With the expansion of transition metal catalysis over the past 50 years, naturally, catalysed conjugate addition reactions have been investigated as a means to improve the utility, regio- and enantio-selectivity and the scope.[88] In particular, studies have been directed towards rhodium,[89] copper[90] and palladium catalysis.[91, 92] Despite the benefits of Pd(II)-catalysis, such as being air and moisture stable and the commercial availability of the catalyst, this area has been considerably underdeveloped compared to rhodium and copper catalysis.[92]

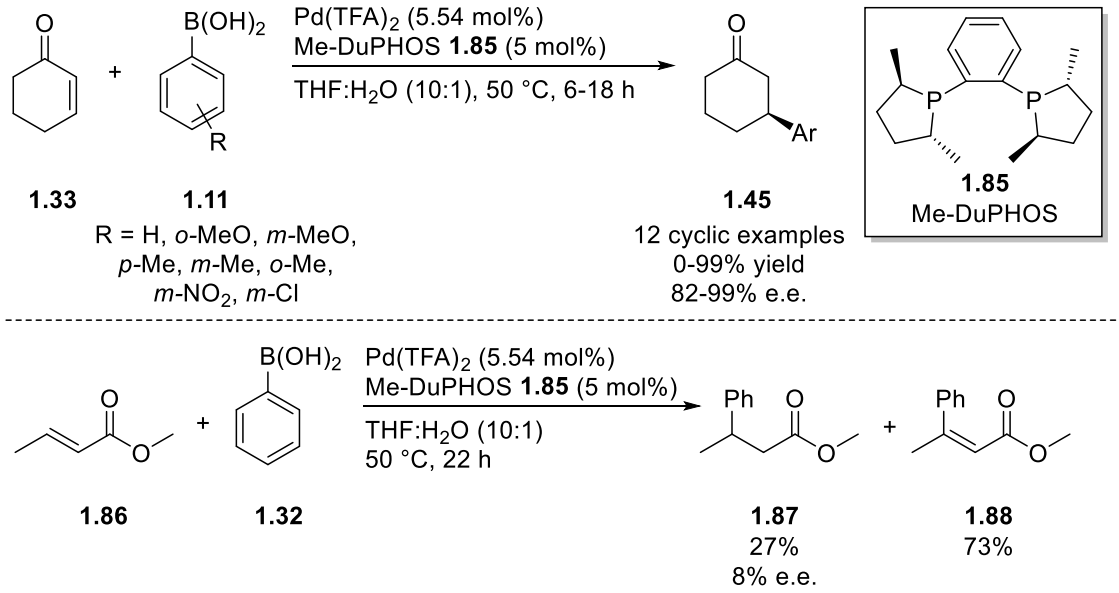
There are many similarities between the Pd(II)-catalysed conjugate addition reaction and the oxidative Heck reaction. These similarities extend to both the reagents and reaction conditions employed but also to the catalytic mechanism of these reactions, and as such the reactions are often in competition with each other.[66] Therefore, it would be appropriate to mention some key papers on this reaction within this review, with a focus on enantioselective Pd(II)-catalysed conjugate addition reactions of conjugate acceptor molecules and organoboron reagents.

As previously mentioned, mechanistically, Pd(II)-catalysed conjugate addition is very similar to the oxidative Heck reaction (Section 1.2.6, Scheme 1.26).[66] Both cycles are thought to be the same, up until the last step. As documented in Sections 1.2.1 and 1.2.6, the oxidative Heck cycle produces the Heck-type product **1.44** *via syn* β-hydride elimination, before re-oxidation to catalytically active Pd(II) species. However, within the conjugate addition cycle, protonolysis is the final step to yield **1.45** (Section 1.26, Scheme 1.26). Furthermore, the conjugate addition cycle is isohypsic at Pd(II) so the catalytically active species is regenerated after protonolysis and no oxidation is necessary. The reagents and conditions employed are therefore very similar, except for the requirement of an external oxidant within the Pd(II)-catalysed oxidative Heck reaction. The Lee group documented that simply switching the solvent can be enough to switch the reactivity from oxidative Heck to conjugate addition, the former preferring more polar aprotic solvents such as DMSO or DMF and the latter, chlorinated solvents such as DCE.[66]

1.4.2 Pd(II)-Catalysed Enantioselective Conjugate Addition Reactions

There has been extensive research into Pd(II)-catalysed enantioselective conjugate addition reactions within recent years,[91, 92] therefore, only key and seminal published works will be highlighted and discussed.

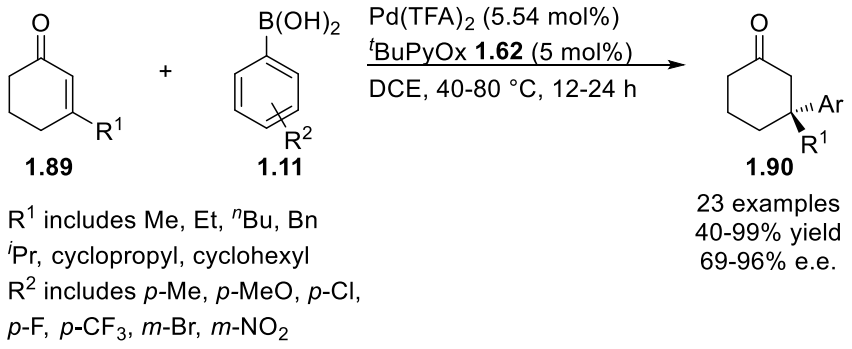
The first asymmetric Pd(II)-catalysed conjugate addition reaction with aryl boronic acids was carried out by Minnaard and co-workers in 2005.[93] Chiral Me-DuPhos **1.85** ligand (5.5 mol%) with $Pd(TFA)_2$ (5 mol%) in THF/H_2O (10:1) at 50 °C successfully catalysed the reaction of aryl boronic acids **1.11** with a range of cyclic ketones and lactones to furnish the enantioenriched conjugate addition product **1.45** in 40–99% yield and up to 99% e.e. (Scheme 1.40). Electron-withdrawing functionalised aryl boronic acids either performed sluggishly (*m*-chlorophenyl) or furnished no desired product (*m*-nitrophenyl). Linear conjugate acceptors were also studied, however, they were less successful. Acyclic ester methyl *E*-crotonate **1.86** did not selectively form the conjugate product **1.87,** instead favouring the formation of oxidative Heck product **1.88** (73% *vs.* 27%, 8% e.e.).



Scheme 1.40: First example of Pd(II)-catalysed asymmetric conjugate addition

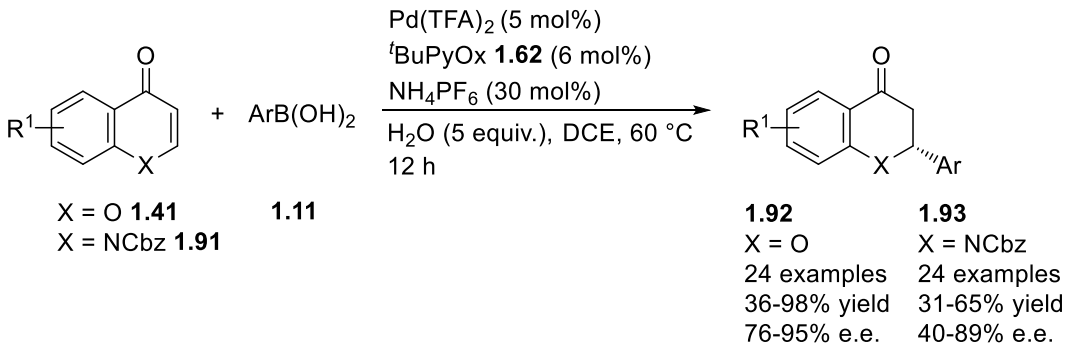
As previously mentioned in Section 1.2.4, *N*,*N*-type ligands are popular ligands for Pd(II) catalysis as much like the catalyst, the ligands are also stable in both air and moisture.[31] Lu and Lin were the first to incorporate the use of chiral (*S*)-PyOx and bisoxazoline (BOX) ligands within Pd(II)-catalysed conjugate addition reactions to

form all-carbon quaternary centres, albeit in poor yields.[94] However, in 2011, Stoltz and co-workers demonstrated the use of ^{t}BuPyOx **1.62** ligands in Pd(II)-catalysed conjugate addition reaction to form all-carbon quaternary centres (Scheme 1.41).[95] 3-Substituted cyclic enones **1.89** were successfully reacted with various aryl boronic acids **1.11** to produce excellent yields of **1.90** (40–99%) in very good enantiomeric excess (69–96% e.e.). This work is impressive considering the steric demand of forming all-carbon quaternary centres enantioselectively. Interestingly, this method is not transferable to the formation of tertiary stereocentres with cyclohexenone **1.33**.[96] The conjugate addition reaction of cyclohexenone **1.33** and phenylboronic acid **1.32** occurs in excellent yield (87%) but very poor e.e. (18%).



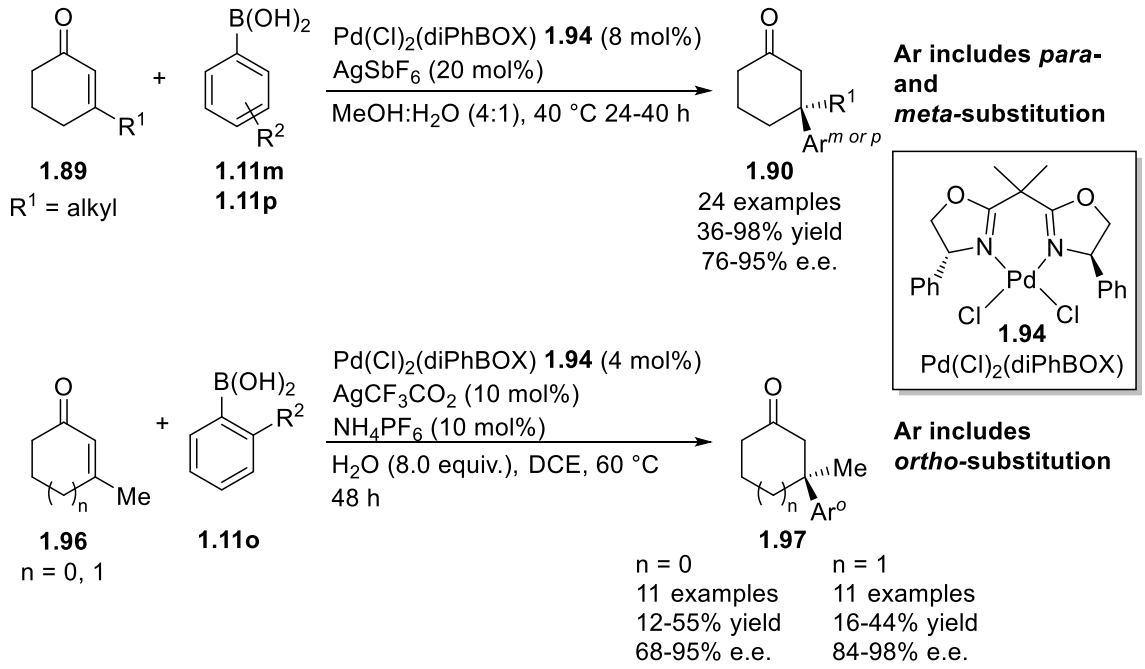
Scheme 1.41: Formation of all carbon quaternary centre through Pd(II)-catalysis

Employing the same reaction conditions as used in their 2011 paper,[95] but with the addition of NH_4PF_6 (30 mol%), saw the successful conjugate addition of aryl boronic acids **1.11** to chromones **1.41** in mediocre to outstanding yields (45-98%) and good enantioselectivities (76-96% e.e., Scheme 1.42).[96] Carboxybenzyl protected 4-quinolones **1.91** (X = NCbz) were also subjected to these reaction conditions but with lower success (31-65% yield, 40-89% e.e.).



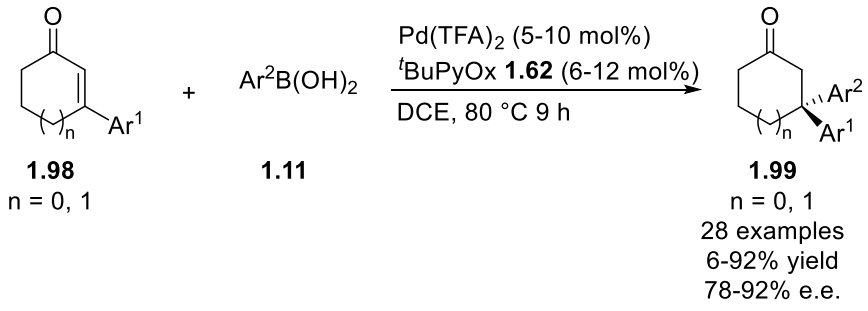
Scheme 1.42: Enantioselective conjugate addition of aryl boronic acids **1.11** and cyclic enones **1.41** and **1.91**

Investigating in the same timeframe as Stoltz *et al*., Minnaard and co-workers similarly reported the construction of all carbon quaternary stereocentres with 3-alkyl substituted cyclic enones **1.89**.[97] The group utilised pre-formed catalytic complex $PdCl_2$(diPhBOX **1.94**) and $AgSbF_6$ as an additive (Scheme 1.43). A variety of *para*- **1.11p** and *meta*-substituted aryl boronic acids **1.11m** were successfully reacted, however, *ortho*-substituted aryl boronic acids **1.11o** were not tolerated under these conditions. However, this limitation was addressed in a future study with slightly modified conditions, adding CF_3CO_2Ag to generate the more active $Pd(TFA)_2$(diPhBOX) catalyst *in situ*. In addition, a slightly increased reaction temperature and time resulted in successful conjugate addition with *ortho*-substituted aryl boronic acids **1.11o** (Scheme 1.43).[98]



Scheme 1.43: Enantioselective conjugate addition studies of Minnaard *et al.*[97, 98]

Successful reactions with 3-aryl substituted cyclic ketones **1.98** had previously been elusive in Pd(II)-catalysed conjugate addition reactions.[63] Stanley *et al.* addressed this drawback in 2017, utilising PyOx ligands and $Pd(TFA)_2$ in DCE (Scheme 1.44).[99] No additives were required to achieve respectable enantioselectivities for a sterically cumbersome reaction. A range of aryl substitution on cyclic alkene **1.98** were tested including heterocycles, and aryls with electron-withdrawing and electron-donating functionality, furnishing up to excellent yields of **1.99** (up to 92%).



Scheme 1.44: Stanley *et al.*'s investigations into enantioselective conjugate additions

1.7 Conclusions

A great deal of research has been carried out into the palladium(II)-catalysed oxidative Heck reaction, especially over the past 2 decades. The oxidative Heck reaction has proven to be compatible with cyclic alkenes and di- and tri-substituted alkenes, all of which are considered challenging coupling partners in the palladium(0)-catalysed Heck reaction. The Pd(II) oxidative Heck reaction also utilises milder reaction conditions and is air and moisture tolerant. The increased recent interest further demonstrates the potential of oxidative Heck coupling, especially for enantioselective synthesis. To improve the efficiency of Pd(II)-catalysis, it would be beneficial to combine it in an auto-tandem catalytic reaction, which has never been applied to an oxidative Heck desymmetrisation reaction. This aim will be the focus of Chapter 2.

Mechanistically related Pd(II)-catalysed conjugate addition reaction has also emerged as a powerful method for the enantioselective installation of all carbon quaternary stereocentres. So far, however, Pd(II)-catalysed conjugate addition has never been exploited in intermolecular enantioselective desymmetrisation reactions, which is the topic of Chapter 3.

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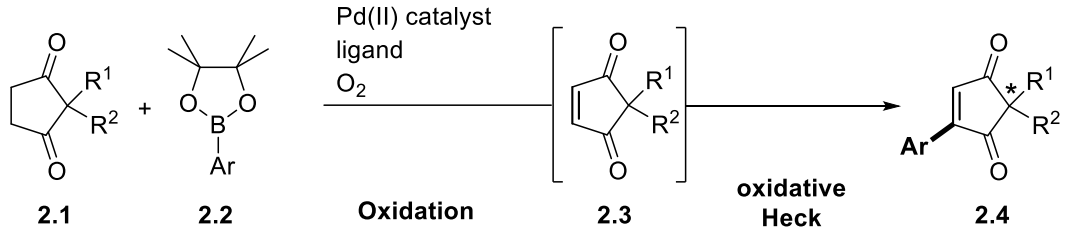
Chapter 2: The Development of an Auto-Tandem Dehydrogenation/Oxidative Heck Desymmetrisation Reaction of 2,2-Disubstituted Cyclopentanediones



- Auto-tandem catalysis: batch and continuous flow
- Pd catalyses two different reactions
- Telescoped synthesis for enantioselective desymmetrisation

Acknowledgements

All work in this chapter was carried out by the author unless clearly marked. The author would like to thank undergraduate summer student Gemma McMurdo (†) and MChem project student Bryan Nderitu (‡) for their contributions to this project. Any work completed by either Gemma or Bryan is clearly indicated by the appropriate symbol.

Gratitude and thanks are also extended to Dr John Tobin and Dr Filipe Vilela for their help and expertise with the continuous flow chemistry.

2.1 Background

The 2,2-disubstituted cyclopentenedione motif **2.3** is prevalent in many natural products and biologically active molecules, such as madindoline A[1] and B,[2] similin A,[3] involutone,[4] ochroleucin A_1[5] and (−)-preussidone (Figure 2.1).[6] Therefore, an efficient catalytic route to molecules of this nature would be synthetically useful.

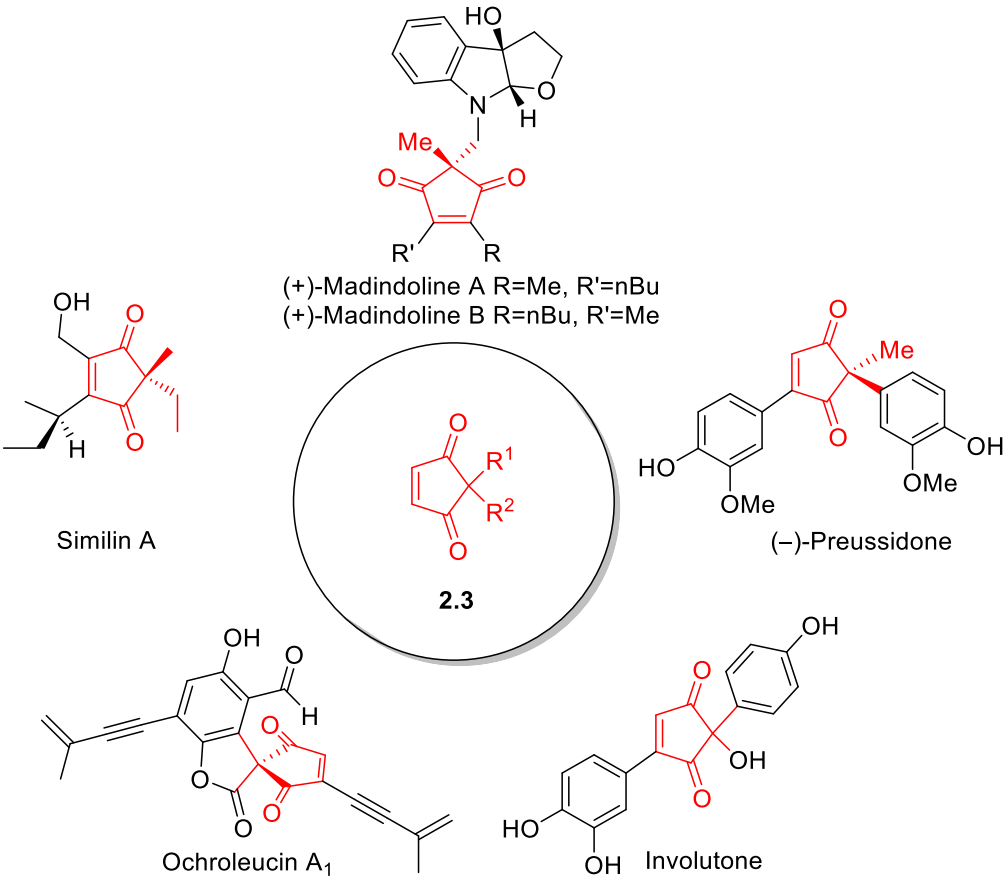
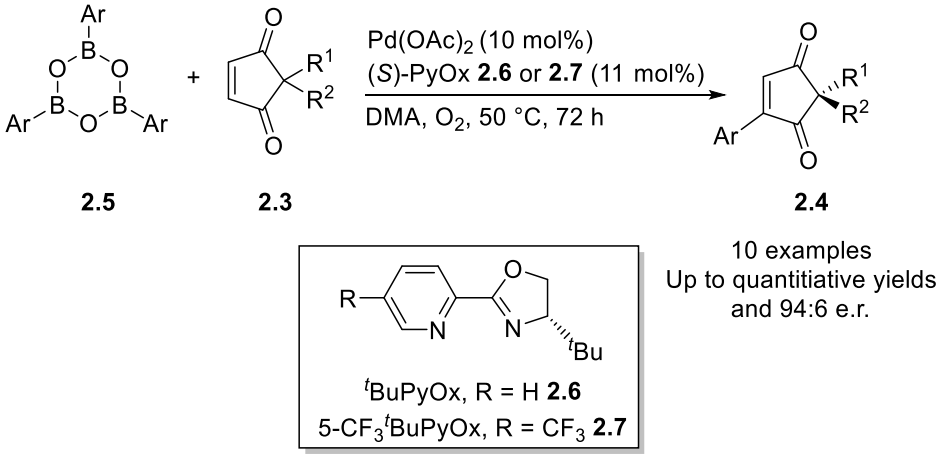


Figure 2.1: Natural products with the 2,2-disubstituted cyclopentenedione motif **2.3**

These cyclic enones **2.3** can contain an all carbon pro-stereogenic centre in the 2-position, but the existence of a plane of symmetry within the molecule makes them achiral. However, this also makes them a perfect candidate for desymmetrisation reactions.[7-9] A desymmetrisation protocol is an attractive alternative for creating quaternary stereogenic centres as the enantioselective reaction does not involve the

formation of an all-carbon quaternary centre. The reaction occurs remote to the pro-stereogenic centre, removing the steric burden from the enantioselective reaction.[9] The importance of desymmetrisation reactions for the generation of quaternary stereogenic centres has recently been highlighted in several review articles. [8-10] Furthermore, the desymmetrisation of 2,2-disubstituted cyclopentenediones **2.3** has been widely investigated in the recent years, including transition metal-[11-13] and organo-catalysed coupling reactions,[14-16] enantioselective cycloadditions,[17-21] and kinetic resolutions.[22]

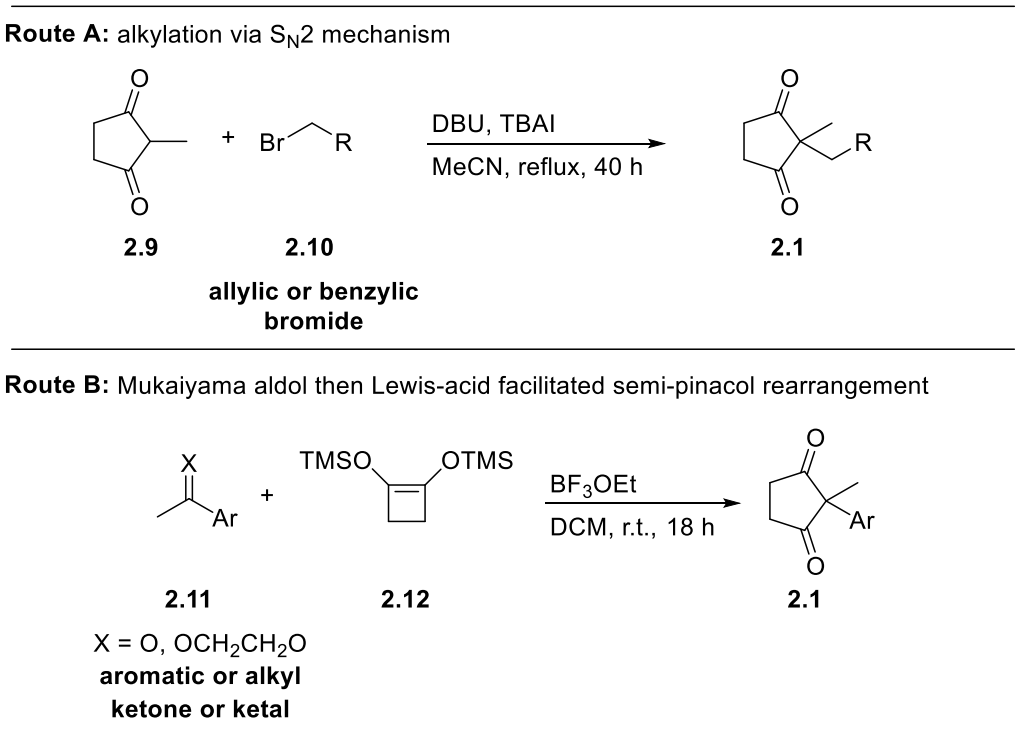
As discussed in Chapter 1, Section 1.3, in 2015, the Lee group published the first Pd(II)-catalysed oxidative Heck desymmetrisation reaction in the literature. It is one of the few examples in the literature where the enedione of the cyclopentenedione remains in place in the product. The group reported the coupling of achiral enediones **2.3** with aryl boroxines **2.5** in up to quantitative yields and 94:6 e.r. (Scheme 2.1). The practicality of this new methodology was also demonstrated in the synthesis of (+)-preussidone in an efficient one step reaction from **2.3** in 85:15 e.r. and 79% yield.



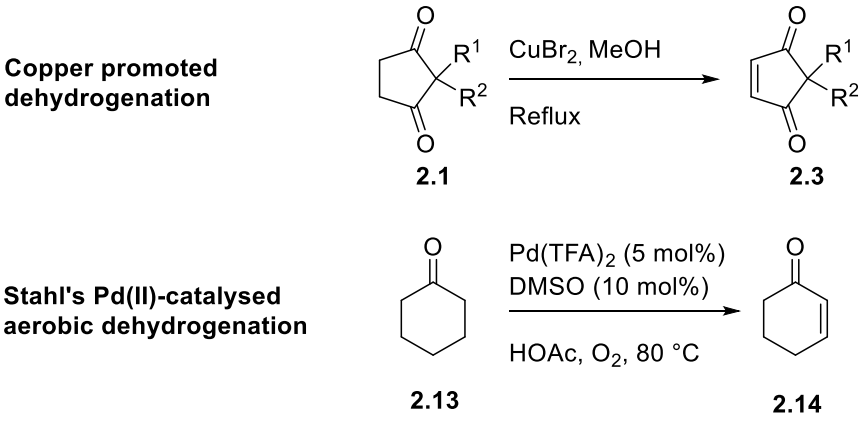
Scheme 2.1: Oxidative Heck desymmetrisation of 2,2-disubstituted cyclopentenediones[12]

The 2,2-disubstituted cyclopentane-1,3-dione precursors **2.1** are easily synthesised from commercially available starting materials. There are two general synthetic routes which

can be followed (Scheme 2.2): an alkylation reaction of 2-methylcyclopentane-1,3-dione **2.9** with an allylic or benzylic bromide[11] **2.10** (route A) or a Mukaiyama aldol followed by Lewis-acid facilitated semi-pinacol rearrangement of a ketone or a ketal **2.11** with bis(trimethoxysiloxy)cyclobutene **2.12** (route B).[11, 23] A copper promoted dehydrogenation can then be carried out to synthesise the corresponding enedione **2.3**.[11, 24] However, this oxidation reaction produces stoichiometric amounts of halogenated waste (Scheme 2.3) and requires another purification step to access **2.3**, neither of which are environmentally friendly.

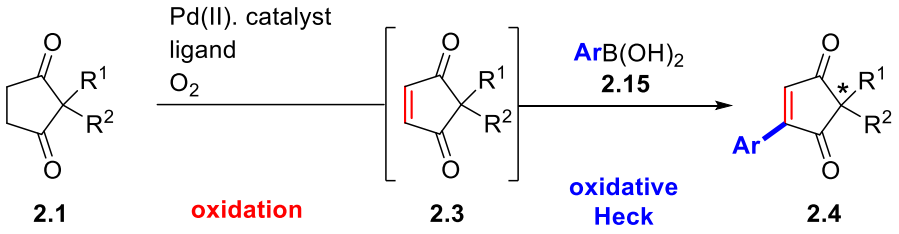


Scheme 2.2: Typical synthetic routes to 2,2-disubstituted cyclopentanediones **2.1**



Scheme 2.3: Cu(II)Br_2 promoted dehydrogenation[11, 24] and Pd(II)-catalysed aerobic dehydrogenation[25]

Stahl and co-workers in 2011 developed an aerobic Pd(II)-catalysed dehydrogenation reaction to efficiently furnish cyclic enones from the corresponding ketone (Scheme 2.3, **2.13** → **2.14**).[25] This publication raises the intriguing possibility of using Pd(II)-catalysis for both the oxidation (**2.1** → **2.3**) and the oxidative Heck reaction (**2.3** → **2.4**) in a one-pot approach (Scheme 2.4). In reactions where the same catalyst can be employed to carry out two mechanistically different transformations within one pot, that reaction can be described as an example of *auto-tandem catalysis* (ATC).[26]



Scheme 2.4: One-pot ATC dehydrogenation/oxidative Heck coupling reaction

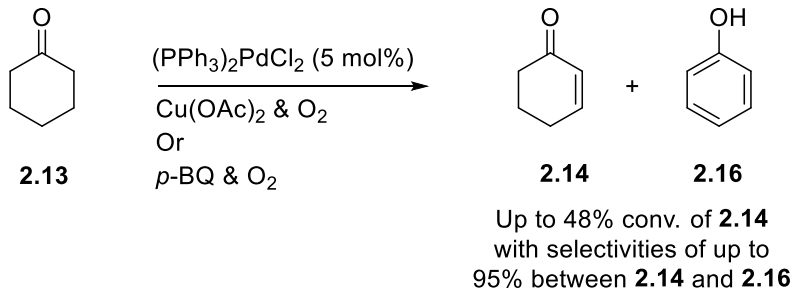
2.1.1 Palladium(II)-Catalysed Oxidation of Cyclic Ketones to Enones

Traditionally, the formation of α,β-unsaturated ketones requires multiple-step syntheses or stoichiometric amount of reagents which is not efficient in time nor atom economy,[27] including several stoichiometric aerobic palladium(II)-facilitated dehydrogenation

reactions of ketones to enones.[28, 29] Therefore, efficient catalytic routes to the formation of enones directly from ketones would be synthetically beneficial since they are employed in many natural product and biologically active molecule syntheses. There have been several review articles within recent years reporting the advances in aerobic Pd(II)-catalysed oxidative reactions.[30-33] For the research discussed in this chapter, it would be pertinent to include a literature review on the development of palladium(II)-catalysed aerobic dehydrogenation reactions, focussing on the oxidation of cyclic ketones to enones.

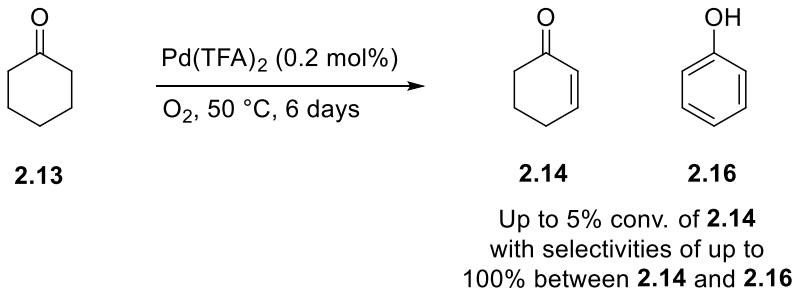
2.1.1.1 Previous developments in aerobic palladium(II)-catalysed dehydrogenation reactions of cyclic ketones

Theissen in 1971 reported the first palladium(II)-catalysed dehydrogenation reaction of cyclohexanone **2.13** to cyclohexenone **2.14.**[34] The reaction was carried out with a Pd(II) catalyst in conjunction with either a Cu(II) salt and O_2 or benzoquinone as a co-catalyst and O_2 (Scheme 2.5). However, conversions were poor (15 – 30%) and selectivities of 80 – 95% between desired enone **2.14** and the corresponding phenol **2.16** were observed. As expected, the activity of the catalyst increased at elevated temperature, but the observed selectivity between enone and phenol decreased. At temperatures above 110 °C, deactivation of the catalyst resulted in a mirror and Pd black depositing on the side of the flask.



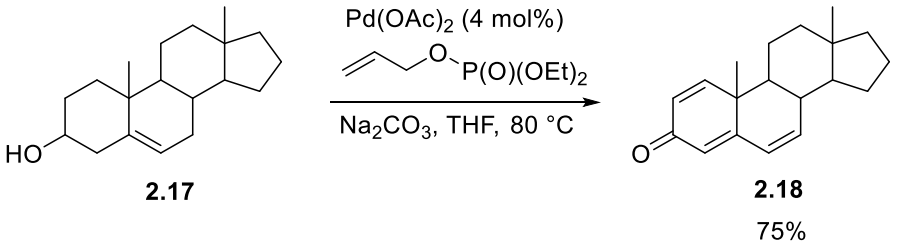
Scheme 2.5: Dehydrogenation of cyclohexanone **2.13** to cyclohexanone **2.14** under Pd(II) catalysis[34]

Muzart and Pete investigated the first Pd(II)-catalysed dehydrogenation of cyclohexanone which relied solely on molecular oxygen to turnover catalyst.[35] However, despite reporting improvements to selectivity for enone **2.14** formation, reaction times were still very inconvenient (up to 6 days, Scheme 2.6) and poor conversions were still observed (up to 11% conv.). Increasing temperature or catalyst loading to 2-10 mol% improved conversion but reduced the selectivity, with significantly more phenol **2.16** being produced. Furthermore, isolated yields of *α,β*-unsaturated ketones had not been disclosed by Theissen[34] or Muzart and Pete.[35]



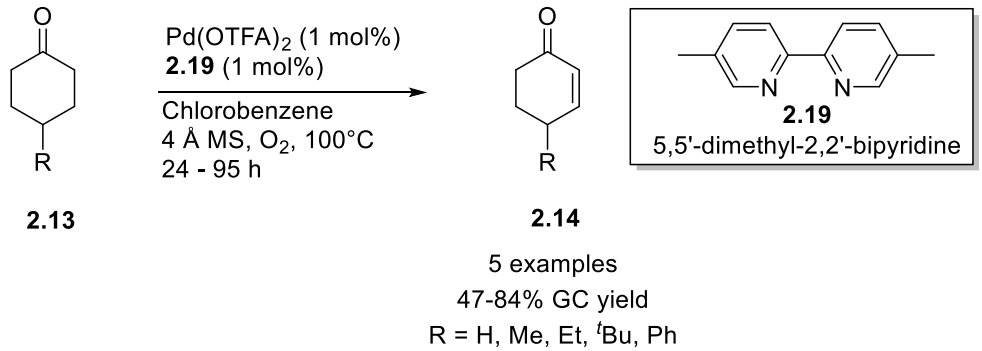
Scheme 2.6: Muzaart and Pete's Pd(II)-catalysed dehydrogenation of cyclohexanone **2.13**[35]

Shvo and Arisha managed to push the development of the palladium(II)-catalysed dehydrogenation reaction further, by introducing base and other oxidants into the reaction mixture (Scheme 2.7).[36] Stoichiometric allyl diethyl phosphate (ADP) and sodium (bi)carbonate were used with a palladium(II) acetate catalyst to achieve poor to good GC yields of the enone products (3-75%). Furthermore, they also document the oxidation of an alcohol to a ketone under the same reaction conditions, followed by dehydrogenation to an α,β-unsaturated ketone as demonstrated with cholesterol-like sterol **2.17** (Scheme 2.7).[36]



Scheme 2.7: The oxidation and dehydrogenation of sterol cholesterol to 2.17[36]

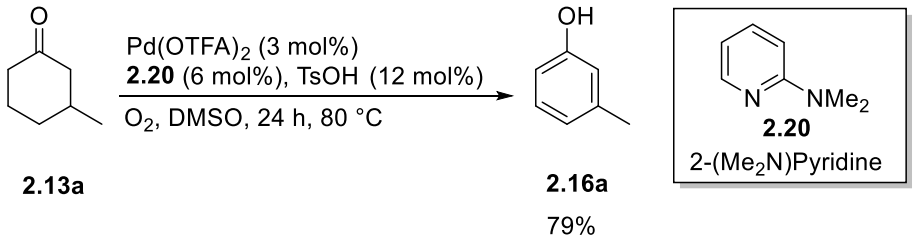
On the other hand, in 2007, Tsuji and co-workers reported a palladium(II)-catalysed protocol with molecular oxygen under base-*free* conditions.[37] Utilising *N*,*N*-ligand 5,5'-dimethyl-2,2'-bipyridine **2.19**, $Pd(TFA)_2$ and 4 Å molecular sieves, an aerobic dehydrogenation of 4-substituted cyclohexanones **2.13** was developed (47-84% GC yield, Scheme 2.8). Only trace amounts of the corresponding phenol were observed. Deactivation of the palladium(II) catalyst was circumvented using ligands, stabilising the Pd(II) complex and avoiding the aggregation of Pd black.[37] This was the first instance in the literature of a useable Pd(II)-catalysed aerobic dehydrogenation protocol of ketones to enones; it is unfortunate that the scope was limited, and only GC yields were recorded.



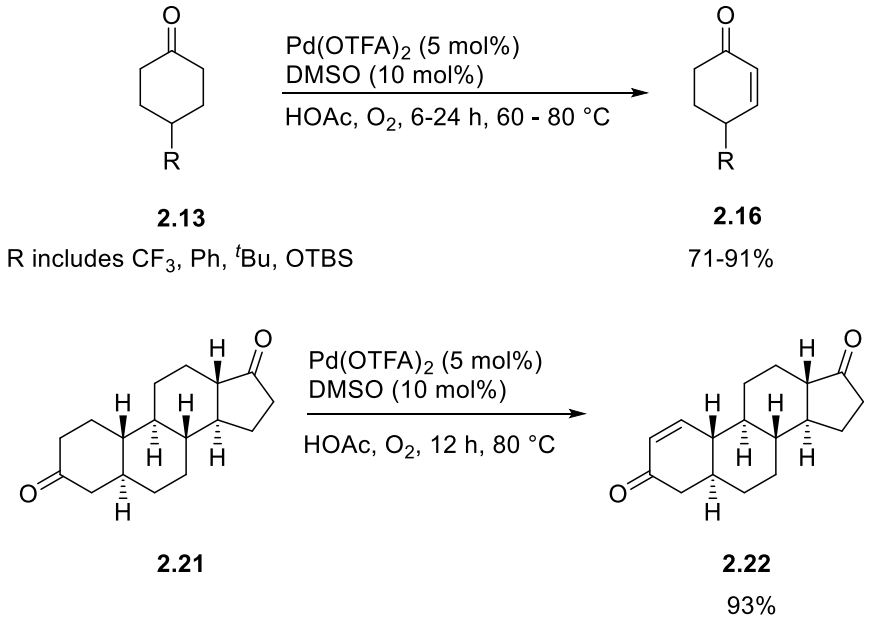
Scheme 2.8: Molecular oxygen facilitated Pd(II)-catalysed dehydrogenation of cyclohexanones **2.13**[37]

2.1.1.2 The contributions of Stahl *et al.* to palladium(II)-catalysed dehydrogenation reactions of cyclic ketones

A robust palladium(II)-catalysed aerobic dehydrogenation protocol was not disclosed until 2011, when Stahl and co-workers first documented their seminal work on the oxidation of cyclohexanones **2.13** all the way to phenols[38] **2.16** (Scheme 2.9) and then chemoselectively to the enone **2.14** (Scheme 2.10).[25] In the latter, employing $Pd(TFA)_2$ (5 mol%), and dimethyl sulfoxide (DMSO, 10 mol%) as ligand in the presence of molecular oxygen, the selective dehydrogenation of cyclohexanone **2.13** was achieved in excellent isolated yield (91%) with minimal phenol **2.16** formation (8%). These optimised conditions were utilised in a varied cyclic substrate scope with moderate to impressive yields (54-93%). Electron-deficient substituents gave faster reaction rates, and flavones were also efficiently constructed from chromones in one step with good yield (66-80%).

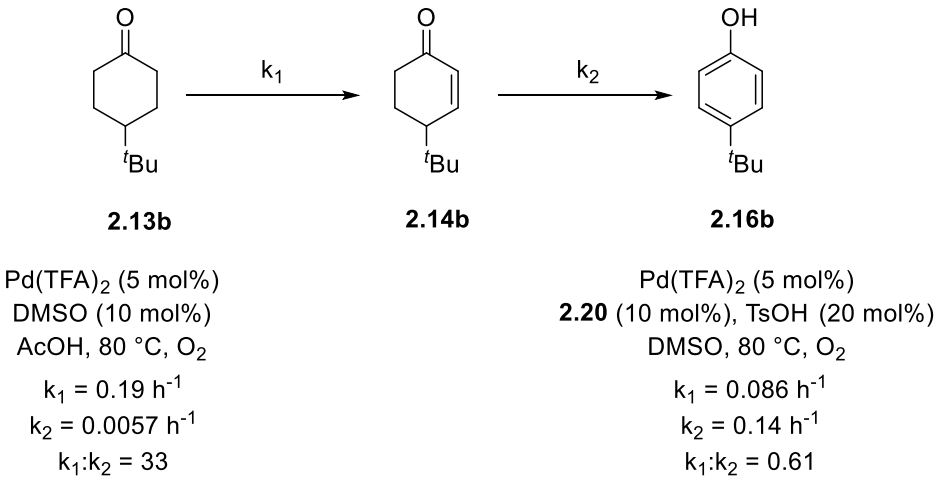


Scheme 2.9: Oxidation of cyclohexanones **2.13** to phenols **2.16**[38]



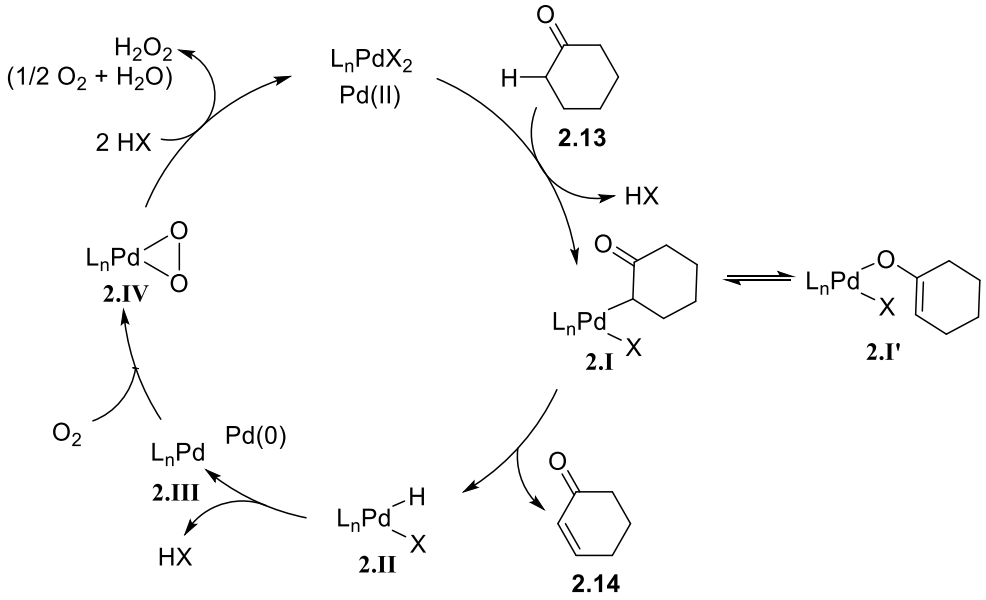
Scheme 2.10: Palladium(II)-catalysed dehydrogenation of cyclic ketones to enones[25]

To account for the increased selectivity of the enone product over the phenol product with the catalyst system employed in this study ([$Pd(TFA)_2$ and DMSO] vs. [$Pd(OTFA)_2$ and **2.20**]), kinetic studies were carried out (Scheme 2.11). A comparison of the time courses for the relative rates of the dehydrogenation step with the two catalyst systems were made. Fitting this data to a sequential model revealed that, with the $Pd(DMSO)_2(TFA)_2$ catalyst, the first step (**2.13b→2.14b**) is 33 times faster than the second step (**2.14b→2.16b)**. Conversely, with $Pd(TFA)_2$(**2.20**), the first dehydrogenation step is nearly 2-fold slower than the second dehydration step to yield the phenol product **2.16b**.



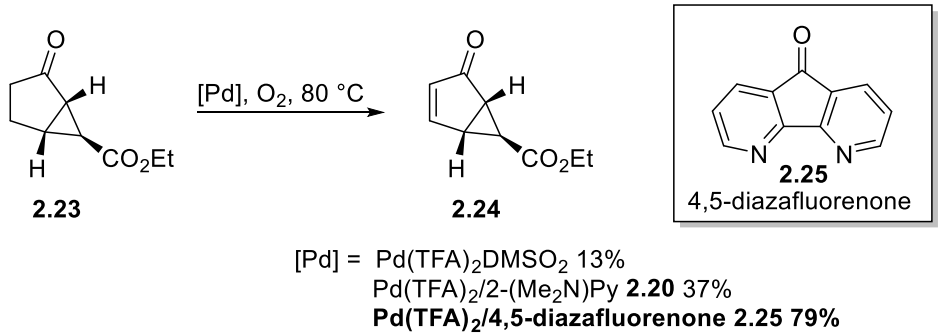
Scheme 2.11: Kinetic studies of the oxidation of cyclohexanones to phenols[25]

Stahl and co-workers postulated that the catalytic cycle proceeds through a Pd(II)-enolate (**2.I** or **2.I′**), followed by *β*-H elimination from **2.I** to yield the dehydrogenation product **2.14** (Scheme 2.12). The resulting Pd(II)-hydride species **2.II** undergoes reductive elimination to **2.III**, which is then aerobically oxidised to regenerate the catalytically active species, through oxo-palladium species **2.IV**. It is also suspected that the hydrogen is lost through hydrogen peroxide.



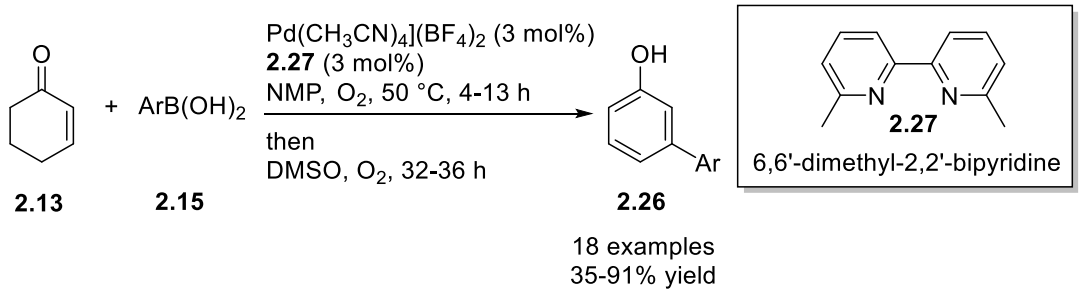
Scheme 2.12: Proposed catalytic cycle for Pd(II)-catalysed dehydrogenation of cyclic ketones[25]

In an effort to address some of the limitations Stahl *at el.* had faced in the above publications, especially the dehydrogenation of bicyclic cyclopentanone **2.23** which is an important precursor to a pharmaceutically important agonist, they sought more effective ligands for the Pd(II)-catalysed aerobic dehydrogenation reaction. Commercially available 4,5-diazafluorenone **2.25** as ligand with $Pd(TFA)_2$ as catalyst was very effective in the dehydrogenation to **2.24** (Scheme 2.13, 79% yield) and even successful in dehydrogenating challenging acyclic ketones and aldehydes.[39]



Scheme 2.13: 4,5-Diazafluorenone **2.25** as effective ligand for challenging dehydrogenation substrates[39]

The group demonstrated the utility of their dehydrogenation protocol by developing an efficient one-pot approach to *meta*-substituted phenols **2.26** (Scheme 2.14), which are difficult to synthesise due to phenols being *ortho*- and *para*-directing.[40] An oxidative Heck reaction is carried out between cyclohexenone **2.13** and an aryl boronic acid **2.15** before the addition of DMSO to push the dehydrogenation to the coupled *meta*-substituted phenol **2.26**. No dehydrogenation to the phenol occurs without the addition of DMSO.



Scheme 2.14: One-pot approach to the synthesis of *meta*-substituted phenols **2.26**[40]

A Pd(II)-catalysed aerobic dehydrogenation reaction of ketones to enones has been developed and advanced, especially by Stahl *et al.* in recent times. These publications demonstrate how sought after useful, direct and efficient catalytical procedures are for key reactions such as forming an enone directly from the ketone.

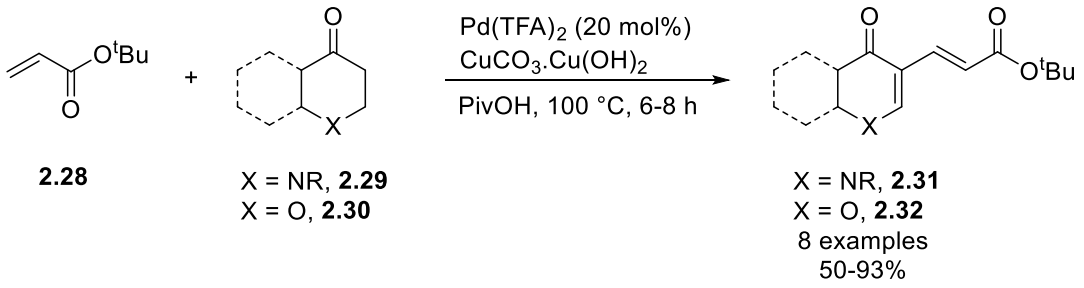
2.1.2 Auto-Tandem Catalysis (ATC)

One-pot multistep reactions which are mechanistically different from each other but are catalysed by the same catalyst (or auto-tandem catalysis (ATC) as defined by Fogg and dos Santos)[26] are an interesting demonstration of just how efficient and green chemistry can be.[41] Not only are expensive transition metal catalysts being employed in multiple steps in one-pot, which is economically beneficial, it also means that solvent used during the reaction and purification is dramatically reduced, and reaction operation is simplified. ATC reactions have become a powerful synthetic tool employed in numerous areas including heterocycle[42] and carbocycle synthesis,[43] cross-metathesis[44] and cycloadditions.[45]

The expansion of palladium(II)-catalysed aerobic dehydrogenation reactions and oxidative Heck reactions over the last four decades, has led to a natural progression to the development of a one-pot aerobic dehydrogenation/oxidative Heck reaction utilising

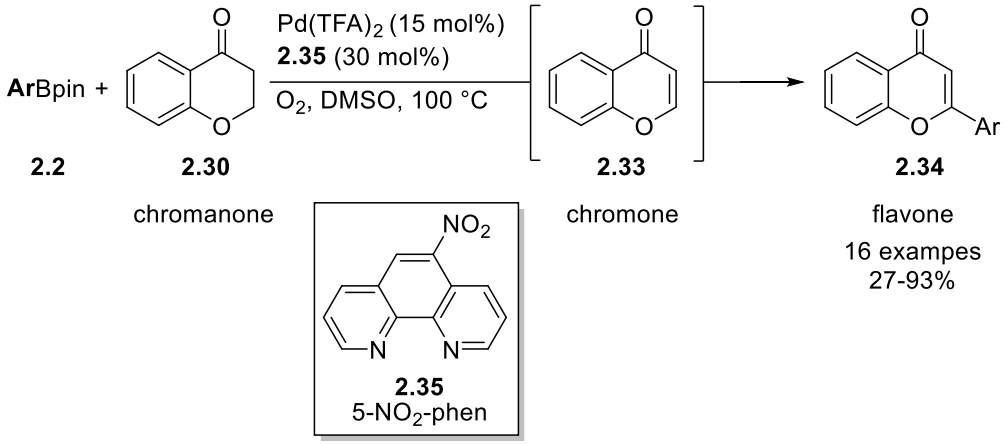
the same palladium(II) catalyst. Some relevant Pd(II)-catalysed dehydrogenation/coupling examples are discussed below.

In 2012, Hong and co-workers published a one-pot dehydrogenation/oxidative coupling approach to the synthesis of **2.31/2.32** (Scheme 2.15).[46] The group employed $Pd(TFA)_2$ and a copper(II) salt in pivalic acid at 100 °C to selectively dehydrogenated and then alkenylated onto the 2-position of **2.29/2.30** (50-93%). They also addressed selectively arylating the 3-positions in the formation of flavones from chromanones **2.30** in moderate to good yield (42-79%).



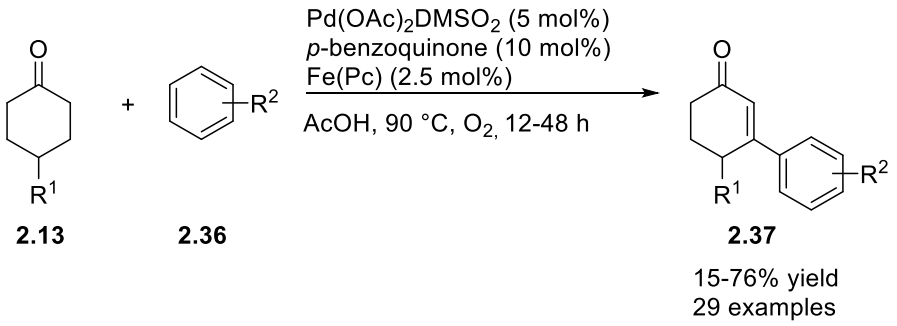
Scheme 2.15: Hong and co-workers Pd(II)-catalysed one-pot dehydrogenation/oxidative coupling reaction[46]

In 2016, Kim and co-workers also investigated an ATC reaction for the formation of aryl substituted flavones **2.34** from chromanones **2.30** using aerobic palladium(II)-catalysed dehydrogenation/oxidative Heck chemistry (Scheme 2.16).[47] Kim *et al.*, overcame the necessity for copper(II) and silver(I) salts required in the dehydrogenation of chromanone **2.30** by employing *N,N*-type ligands such as 5-NO_2-phen **2.35**. Coupling with aryl pinacol boronic esters **2.2** successfully furnished flavones **2.34** in poor to excellent yields (27-93%). A chromanone **2.30** scope was also carried out successfully, varying the electronics and substitution provided good yields (51-85%). Furthermore, the direct and facile synthesis of natural flavones apigenin and luteoline was demonstrated in one step each from the readily available chromanone.



Scheme 2.16: Kim and co-workers palladium(II) catalysed aerobic dehydrogenation/oxidative Heck ATC reaction[47]

Bäckvall and co-workers developed an elegant ATC Pd(II)-catalysed aerobic double dehydrogenation Fujiwara–Moritani coupling reaction of arenes **2.36** and cyclohexanones **2.13** to yield substituted α,β-unsaturated cyclic ketones **2.37** in one pot (Scheme 2.17).[48] The group exploited biomimetic oxidation pathways to improve the re-oxidation of the Pd(II)-catalyst with catalytic amounts of *p*-benzoquinone (10 mol%), iron phthalocyanine (Fe(Pc)) (2.5 mol%) and stoichiometric molecular oxygen in acetic acid at 90 °C. In this instance, the molecular oxygen is not thought to directly re-oxidise the Pd(II)-catalyst, the *p*-benzoquinone is thought to reoxidise the Pd(0) species back to Pd(II); Fe(Pc) is then thought to re-oxidise the hydroquinone back to the benzoquinone and finally the molecular oxygen is thought to re-oxidise the Fe(Pc). The coupled products **2.37** were obtained in poor to very good yields; however, the selectivity is generally poor when there is a choice of position to activate on the arene **2.36**.



Scheme 2.17: Pd(II)-catalysed dehydrogenation/Fujiwara-Moritani/dehydrogenation to form compounds **2.37**

These examples all demonstrate that there is an interest to develop aerobic Pd(II)-catalysed dehydrogenation/coupling ATC reactions.

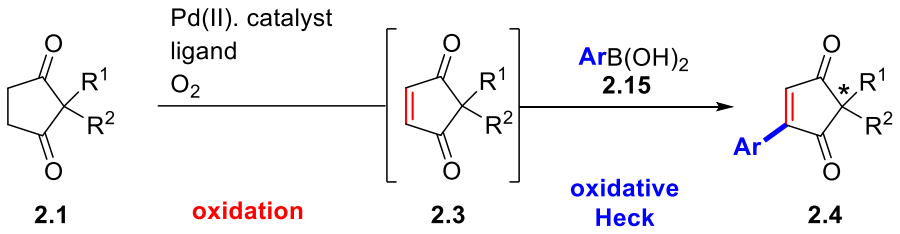
2.2 Project Aims

As mentioned in Section 2.1, combining Pd(II)-catalysed aerobic dehydrogenation reactions with Pd(II)-catalysed oxidative Heck couplings in one-pot would lead to the development of an auto-tandem catalytic reaction (ATC), where an ATC reaction is described as employing the same catalyst for two mechanistically different transformations within one-pot.[26, 41]

Palladium(II)-catalysed aerobic dehydrogenation/coupling ATC reactions had been developed previously by groups of Kim[47], Hong[46] and Bäckvall[48] but none of these publications involved carrying out an *enantioselective* ATC dehydrogenation/coupling reaction.

Our aim for this project was therefore to develop an ATC dehydrogenation/oxidative Heck coupling reaction of 2,2-disubstituted cyclopentenediones **2.1**, first investigating the unknown racemic desymmetrisation ATC reaction and then expanding the study to an enantioselective desymmetrisation ATC reaction (Scheme 2.18). To increase the

applicability of this reaction, we also aim to investigate the reaction in continuous flow as well as batch.



Scheme 2.18: Project aim to develop the first enantioselective Pd(II) enantioselective ATC dehydrogenation/oxidative Heck reaction

2.3 Optimisation of a Racemic One-Pot Dehydrogenation/ Oxidative Heck

2.3.1 Optimisation of the Dehydrogenation Reaction

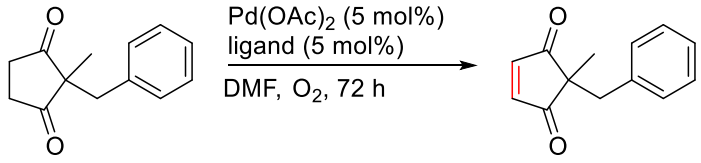
Our efforts were initially directed towards optimising the dehydrogenation reaction. Unlike the Kim paper,[47] where a dehydrogenation reaction of chromanones **2.30** to chromones **2.33** had already been demonstrated by Stahl,[25] the Pd(II)-catalysed aerobic dehydrogenation of cyclopentanediones **2.1** had, to the best of our knowledge, not been reported. Since the optimised conditions for the oxidative Heck reaction had previously been established,[12] for this one-pot process to be successful then the optimised conditions of the dehydrogenation reaction had to be similar to those of the oxidative Heck reaction. The options for the optimisation of the dehydrogenation reaction therefore became limited. The source of palladium, $Pd(OAc)_2$ and the type of ligand, *N*,*N*-type ligands, had to be kept consistent to ensure that the oxidative Heck reaction would still proceed. Furthermore, only polar aprotic solvents would be appropriate for the coupling reaction i.e. *N*,*N*-dimethylformamide (DMF) or *N*,*N*-dimethylacetamide (DMA).[12] Dimethylsulfoxide (DMSO), although popular for other oxidative Heck reactions as proposed by Stahl[25] and Kim papers,[47] would be too chelating and could

hinder ligand binding to the catalyst. With the prospect of an enantioselective reaction in mind, this was discounted as a choice of solvent.

As **2.3** is the intermediate product of the one-pot two-step reaction and will not be isolated in the final optimised reaction, we focused on pushing the conversion of **2.1→2.3** as high as possible during the optimisation of the dehydrogenation reaction. As such, results in the optimisation of the dehydrogenation reaction will be quoted in %conversion, calculated from ^{1}H NMR analysis of the crude reaction mixture, unless otherwise stated.

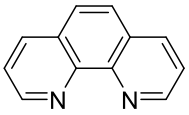
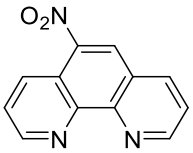
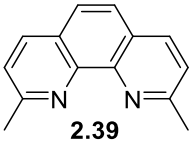
Using established racemic oxidative Heck conditions of $Pd(OAc)_2$ (5 mol%) as catalyst and 1,10-phenanthroline (1,10-phen) **2.38** as ligand in DMF as a starting point, at 70 °C only traces of dehydrogenation product were observed after 72 h (Table 2.1, entry 1). Increasing the reaction temperature to 100 °C improved conversion to 50% (entry 2). A screen of different 1,10-phenanthroline ligands at 100 °C was then investigated. 2,9-Dimethyl-1,10-phenanthroline (dmphen) **2.39** (entry 4) and 5-NO_2-phen **2.35** (entry 3) were studied, with dmphen **2.39** performing considerably better than the others (74%). Unfortunately, and predictably, use of dmphen **2.39** which was not conducive to the oxidative Heck reaction in the previous desymmetrisation paper (Scheme 2.1),[12] yielded only trace amounts of oxidative Heck coupled product **2.4aa** when a one-pot reaction was attempted with *p*-methoxyphenyl boroxine **2.5a** (Scheme 1.19).

Table 2.1: 1,10-Phenanthroline type ligand screen at various temperatures

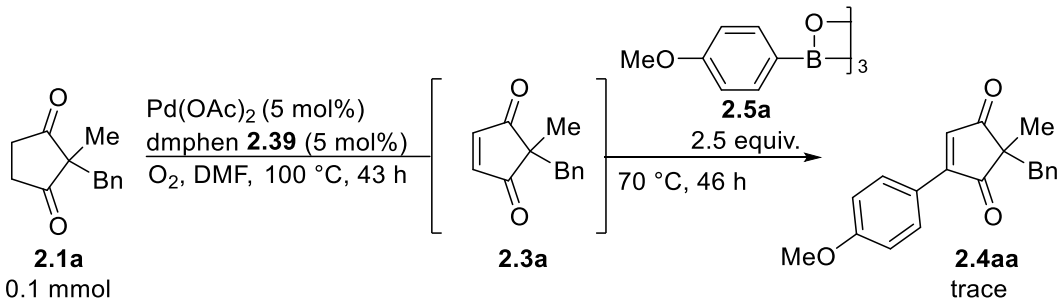


2.1a
0.1 mmol

2.3a

Entry[a]	Ligand	Temp (°C)	Conversion (%)[b,c]
1	 **2.38**	70	trace
2	**2.38**	100	50
3	 **2.35**	100	18
4	 **2.39**	100	74
5	**2.38**	120	72

[a] Reactions carried out under dry conditions. [b] Conversion calculated from comparison of integrations of starting material and product signals in ^{1}H NMR spectra. [c] Conversion after 72 h.



2.1a
0.1 mmol

2.3a

2.4aa
trace

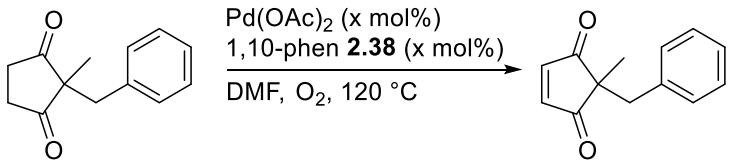
Scheme 2.19: One-pot oxidation/oxidative Heck optimisation with dmphen **2.39**

We therefore focused our optimisation study on 1,10-phen **2.38** as ligand. Pleasingly, increasing the reaction temperature to 120 ℃ promoted the dehydrogenation reaction to 72% in 72 h (Table 2.1, entry 5).

Unfortunately, all attempts to apply the best dehydrogenation conditions to the one-pot ATC reaction **2.1a→2.4aa** were unsuccessful, with the first step often being inconsistent and not going to completion, which impacted the overall yield of the ATC reaction. To overcome this, we investigated the catalyst and ligand loading for the dehydrogenation reaction.

Increasing catalyst and ligand loading to 10/11 mol% had a positive result, resulting in 100% conversion and an 85% isolated yield of **2.3a** after 48 h (Table 2.2, entry 2). Unfortunately, when these conditions were applied to the one-pot ATC reaction, another story of inconsistent and non-reproducible dehydrogenation emerges. We hypothesised that at the increased reaction temperature of 120 ℃, the catalyst/ligand complex was not stable, with palladium black frequently precipitating out and coating the reaction flask. To combat this, we increased the ligand loading to 20 mol% to ensure the palladium catalyst was always ligated (Table 2.2, entry 3). Pleasingly, this pushed the reaction to 100% conversion in an improved reaction time of 18 h, and this reaction was successfully replicated by summer student G. McMurdo.†[49]

Table 2.2: Effects of increased catalyst and ligand loading on the dehydrogenation reaction



2.1a
0.1 mmol

2.3a

Entry[a]	$Pd(OAc)_2$ (mol%)	2.38 (mol%)	Time (h)	Conversion (%)[b]	Yield (%)[c]
1	5	5	72	72	n.d.[d]
2	10	10	48	100	85
3	10	20	18	100	n.d.[d]

[a] Reactions carried out under dry conditions. [b] Conversion calculated from comparison of integrations of starting material and product signals in ^{1}H NMR spectra. [c] Isolated yield. [d] Not determined.

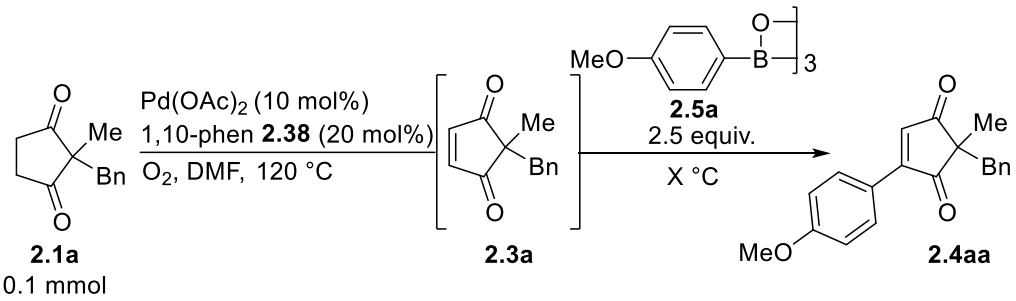
2.3.2 Application of Optimised Dehydrogenation Conditions to the ATC Reaction

Aryl boroxines were chosen as the aryl coupling partner for the ATC reaction optimisation reactions as they were successfully employed in our previous oxidative Heck research.[12] Aryl boroxines are often chosen for coupling reactions as they allow for a slower release of the corresponding boronic acid into the reaction.[50] The boroxine **2.5a** used for these couplings, was dehydrated in a separate flask from the corresponding boronic acid **2.15a** under vacuum (with a heat gun) until all visible condensation had been driven off, before being quickly weighed out in the atmosphere.

Any attempts to add the aryl boroxine **2.5a** before the dehydrogenation reaction had gone to completion resulted in the first step stalling, which then resulted in poor yields of the final oxidative Heck product **2.4aa**. Increased homo-coupling and phenol side products were also observed.

To overcome the issue of the boroxine perhaps being too active to allow the oxidative Heck reaction to go to completion, portionwise addition of the boroxine **2.5a** was attempted after the first step (**2.1**→**2.3**). However, this also failed to push the oxidative Heck reaction to completion (Table 2.3). Employing portionwise addition of 2 then 1.5 equivalents a while later, with various oxidative Heck reaction temperatures (entries 1-3) did not push the oxidative Heck yield above 41% (entry 1). *p*-Benzoquinone was also investigated as an oxidant, with the dehydrated boroxine **2.5a** and the flask evacuated of O_2 and back filled with argon. However, this resulted in the yield lowering (entry 4, 28%). Lastly, we tried making an anhydrous solution of boroxine **2.5a** in DMF so that it would never encounter the water in the atmosphere (during weighing), but unfortunately again, this only resulted in a worse yield of **2.4aa** (entry 5, 26%).

Table 2.3: Attemps to push one-pot reaction to completion under optimised dehydrogenation conditions



Entry[a]	Time (h)	Ox Heck T (X °C)	Boroxine (equiv.)	Yield(%)[b]		
				2.4aa	2.3a	2.1a
1	29 + 76	100	2 (29 h) then 1.5 (46 h)	41	21	-
2	22 + 73	120	2 (22 h) then 1.5 (29 h)	37	35	-
3	16.5 + 68.5	70	2 (16.5 h) then 1.5 (37 h)	40	41	-
4[c]	20 + 68	120	2 (20 h) then 1.5 (47.5 h)	28	40	-
5[d]	20 + 68	120	1.5 (20 h) then 1.5 (47.5 h)	26		-

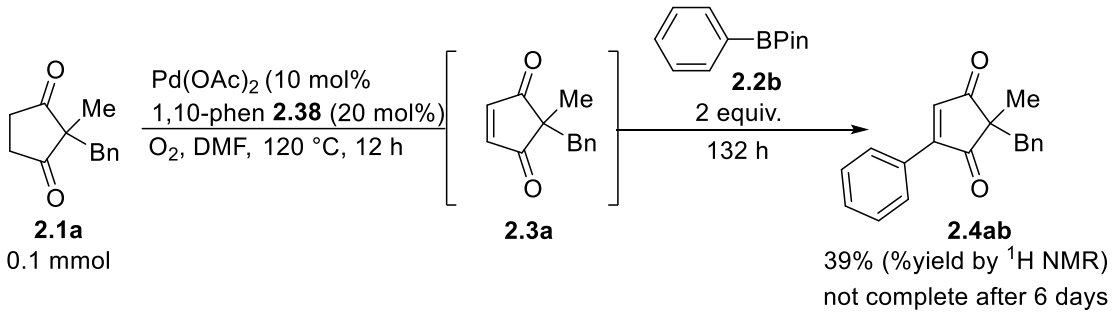
[a] Reactions carried out under dry conditions. [b] Determined by ^{1}H NMR analysis with 1,3,5-trimethoxybenzene as internal standard. [c] *p*-Benzoquinone (1 equiv.) added with the second addition of boroxine (47.5 h) under an inert atmosphere. [d] Dehydration carried out on a scale of 0.1 mmol in 1 mL, boroxine dehydration in flask and prepared as an anhydrous solution in DMF.

The oxidative Heck reaction went to completion during our previous studies[12] so we hypothesised that the issue may lie with the dehydrogenation reaction. Analysing the proposed reaction mechanism from the dehydrogenation reaction by Stahl and co-workers,[25] it is thought that the H_2 is lost from the system in the form of hydrogen peroxide (Section 2.1.1, Scheme 2.13). Hydrogen peroxide is known to interact with boronic acids in a Pd(II)-catalysed system in the presence of a molecular oxygen

environment to promote homo-coupling and phenol formation.[50] Although boroxines are less reactive than boronic acids, they do allow a slow release of boronic acid into the reaction. However, as this reaction is run at a higher temperature, at a higher catalyst and ligand loading than the original paper, and potentially in the presence of stoichiometric amounts of hydrogen peroxide which was not present in our original oxidative Heck study, it is plausible to expect that aryl boroxines are too reactive for the ATC reaction to be successful.

2.3.3 Investigations with Aryl Pinacol Boronic Esters

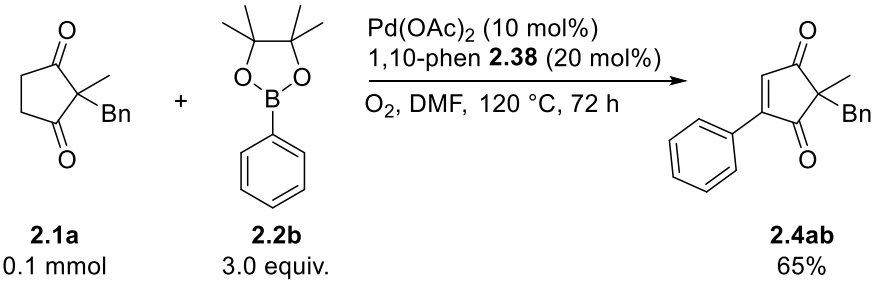
In our attempts to solve the incomplete oxidative Heck reaction problem, we wanted to investigate other aryl boron coupling partner sources. Pinacol boronic esters (Bpin) **2.2** are a much less reactive source of aryl coupling partners,[50] and are less likely to undergo homo-coupling and phenol formation under aerobic palladium(II) catalysis. Initially, the use of an aryl pinacol boronic ester **2.2** was investigated by G. McMurdo, a summer undergraduate student,†[49] where **2.2b** was added after dehydrogenation of **2.1a**→**2.3a** was complete (12 h, Scheme 2.20). However, this led to only 39% oxidative Heck yield after 6 days.



Scheme 2.20: Initial investigations with pinacol boronic ester **2.2b** by G. McMurdo†[49]

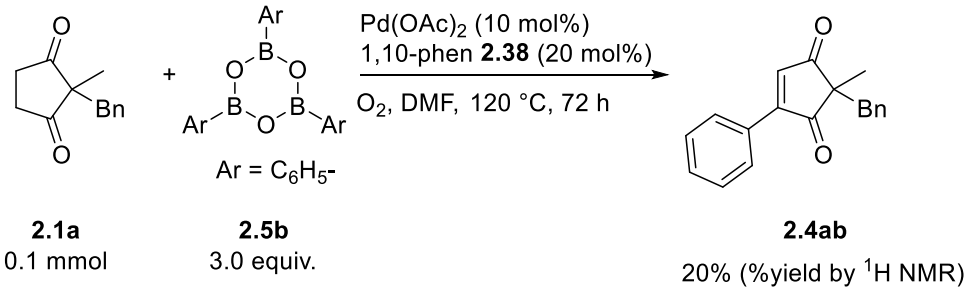
Although the reaction did not go to completion, there was still potential in using aryl pinacol boronic esters **2.2**. We had previously observed that the dehydrogenation step

would not go to completion after the addition of boroxines **2.5**, however, we did not know if this would be the case for pinacol boronic esters **2.2**. We, therefore, attempted the reaction again under optimised dehydrogenation conditions, adding 3 equivalents of phenyl pinacol boronic ester **2.2b** at the start of the reaction. This successfully furnished the oxidative Heck coupled product **2.4ab** in a good yield of 65% with no dione **2.1a** and endione **2.3a** present (Scheme 2.21). Not only had dehydrogenation and oxidative Heck been pushed to full conversion with good yield, but the reaction reached completion in three days. This is the same length of time that the oxidative Heck reactions took in the original paper,[12] and here two transformations have been achieved in one-pot. The efficiency had therefore been increased greatly.



Scheme 2.21: One-pot dehydrogenation/oxidative Heck coupling reaction

To ensure that this procedure cannot be applied to boroxines **2.5**, we carried out a reaction where the boroxine was dehydrated in the reaction flask, followed by the addition of all other reactants. Here the test reaction was carried out with phenyl boroxine **2.5b** to be consistent with the reaction shown in Scheme 2.20. The dehydrogenation reaction went to full completion, further validating the conditions for that portion of the reaction, however, only a poor yield oxidative Heck product **2.4ab** (20%) was recorded (Scheme 2.22).



Scheme 2.22: ATC reaction with the addition of boroxine at the start

2.4 Aryl pinacol boronic ester scope

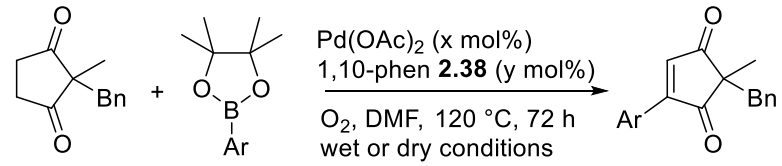
2.4.1 Dry *versus* wet conditions

With optimised conditions in hand (Scheme 2.21), we proceeded to investigate the aryl pinacol boronic ester **2.2** scope, under the optimised dry conditions. Unfortunately, these conditions were not applicable to other pinacol boronic esters (Table 2.4). The coupling of **2.3** with *p*-methoxyphenyl pinacol boronic ester **2.2a** (entry 1) and *p*-bromophenyl pinacol boronic ester **2.2c** (entry 4) only resulted in a poor yield of 43% and 34% respectively. Increasing the $Pd(OAc)_2$ loading to 15 mol% and 1,10-phen **2.38** to 30 mol% did not help either (entries 2 and 5, 45 and 35%, respectively).

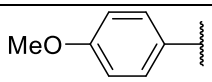
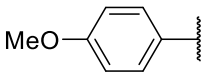
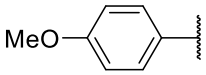
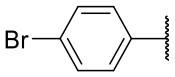
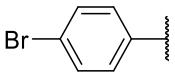
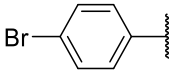
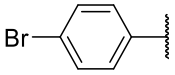
Pinacol boronic esters **2.2** are a less reactive coupling source than boronic acids **2.15** or boroxines **2.5**.[50] Under dry conditions, with the exception of the privileged case of phenyl pinacol boronic ester **2.2b**, it was thought that the low yields were a result of the aryl Bpin **2.2** struggling to transmetallate in the absence of a base. In our desire to keep this a base-free protocol, we tried "wet" conditions. Glassware was not vigorously dried and dry solvent was not used, in the hope that the residual water in the solvent and glassware would be enough to promote transmetallation. Pleasingly, this worked well (entries 3 and 7) where the *p*-methoxyphenyl **2.2a** and *p*-bromophenyl **2.2c** coupled products were both obtained in much-improved yields of 77% and 68% respectively.

The *p*-bromophenyl Bpin **2.2c** required a higher catalyst and ligand loading due to being electron withdrawing (Table 2.9, entries 6 and 7, 35% vs. 68%)

Table 2.4: Comparison of wet and dry conditions with pinacol boronic esters



2.1a 0.1 mmol | **2.2** 3.0 equiv. | **2.4**

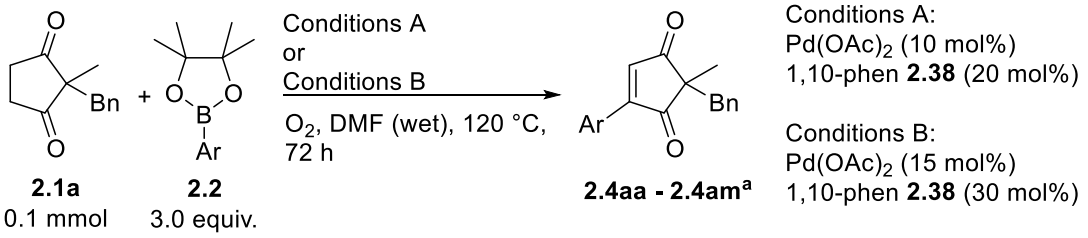
Entry	Ar	Dry or wet conditions[d]	$Pd(OAc)_2$ (x mol%)	Ligand (y mol%)	Yield (%)
1		dry	10	20	**2.4aa,** 43[b]
2[a]		dry	15	30	**2.4aa,** 45[b]
3		wet	10	20	**2.4aa,** 77[c]
4		dry	10	20	**2.4ac,** 34[c]
5		dry	15	30	**2.4ac,** 35[c]
6		wet	10	20	**2.4ac,** 35[b]
7		wet	15	30	**2.4ac,** 68[c]

[a] Reaction carried out by B. Nderitu.[‡51] [b] Determined by ^1H NMR spectroscopy with 1,3,5-trimethoxybenzene as internal standard. [c] Isolated yield. [d] Dry conditions carried out with DMF from SPS, glassware dried and back filled with Ar during reagent additions. Wet conditions with bench top DMF from Sigma Aldrich with non-dried glassware.

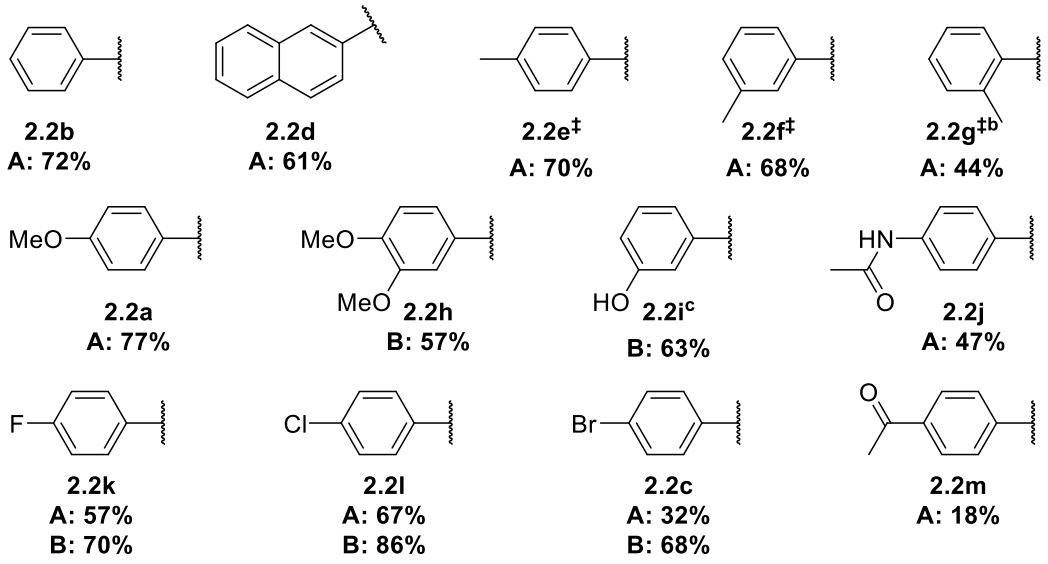
2.4.2 Aryl Pinacol Boronic Ester Scope

The newly optimised wet conditions (conditions A) were more translatable to the aryl pinacol boronic ester **2.2** scope. Phenyl Bpin **2.2b** performed slightly better under wet conditions with the yield improving to 72% (Table 2.5). Furthermore, 2-naphthyl Bpin **2.2d** was also well tolerated, with the reaction proceeding to 61% yield. For less reactive substrates, increasing catalyst and ligand loading to 15 mol% and 30 mol% respectively (conditions B) helped to improve yields. *Para*- **2.2e**, and *meta*-methylphenyl Bpin **2.2f** coupled with no issue, whereas *ortho*-methyl substitution **2.2g** performed more sluggishly presumably due to sterics and required an addition 5 mol% catalyst after 72 h.[‡51] Electron-donating substituents *p*-methoxy **2.2a**, *m*,*p*-dimethoxy **2.2h** and *m*-hydroxy **2.2i** phenyl pinacol boronic esters were all tolerated in the reaction and successfully furnished the oxidative Heck product in moderate to good yield (57-77%). Halogenated pinacol boronic esters proceeded very well through the one-pot reaction (*p*-fluoro **2.2k** 70%, *p*-chloro **2.2l** 86%, *p*-bromo **2.2c** 68%). To our delight, there was no evidence of transient Pd(0) oxidatively adding into the C–Br of the *p*-bromophenyl Bpin **2.2c**, further demonstrating the synthetic use of this reaction. Unfortunately, ketone **2.2m** and acetanilide **2.2j** substituted oxidative Heck product could only be obtained in low (**2.4am**, 18%) and moderate yields (**2.4aj**, 47%). Attempts were made to push these aryl Bpin substrates, including employing conditions B, portionwise addition of ligand and catalyst and portionwise addition of the aryl Bpin **2.2** but none of these improved the yield above what conditions A provided.

Table 2.5: Aryl pinacol boronic ester scope under "wet" optimised conditions



2.1a 0.1 mmol + **2.2** 3.0 equiv. → **2.4aa - 2.4am**[a]



2.2b A: 72%

2.2d A: 61%

2.2e‡ A: 70%

2.2f‡ A: 68%

2.2g‡[b] A: 44%

2.2a A: 77%

2.2h B: 57%

2.2i[c] B: 63%

2.2j A: 47%

2.2k A: 57% B: 70%

2.2l A: 67% B: 86%

2.2c A: 32% B: 68%

2.2m A: 18%

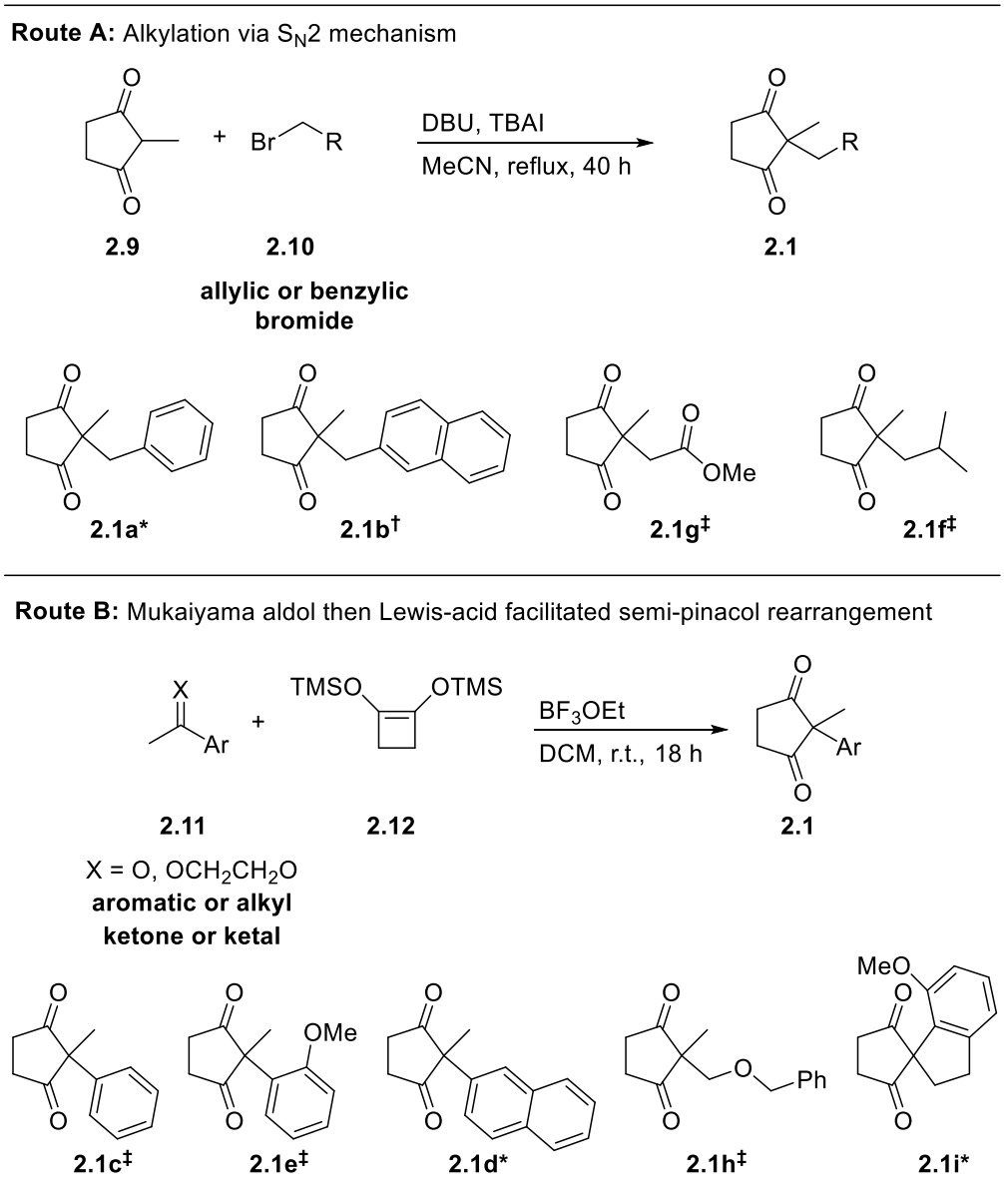
[a] Isolated yields. [b] Further portion of $Pd(OAc)_2$ (5 mol%) required after 72 h and left to react for a further 20 h. [c] %Yield determined by analysis with ^1H NMR spectroscopy by comparison to internal standard 1,3,5-trimethoxybenzene. ‡ Work completed by B. Neritu.

Side-production of phenol became more of a problem with this project than with the previous oxidative Heck project using 2,2-disubstituted cyclopentenediones **2.3**.[12] Although pinacol boronic esters **2.2** are less reactive than boronic acids **2.15** or boroxines **2.5**, the first dehydrogenation step and the elevated temperatures are not present within our original works and perhaps the inclusion of the first dehydrogenation reaction has made the formation of phenol much more likely. The phenol would often co-elute with several of the coupled products **2.4**. Fortunately, either washing with saturated potassium carbonate or treatment with a polymer supported carbonate was sufficient to remove the phenol after purification by silica gel column chromatography.

2.5 2,2-Disubstituted cyclopentanedione scope

2.5.1 Synthesis of 2,2-disubstituted cyclopentanediones

The synthesis of 2,2-disubstituted cyclopentanedione substrates **2.1** was undertaken by various members of the Lee group during this project and the previous project.[12] As mentioned in Section 2.1, two general literature routes were followed directly or adapted to synthesise all substrates used: S_N2 alkylation with allylic or benzylic bromides (Route A, Scheme 2.23)[11] or via a Mukaiyama aldol followed by a Lewis-acid facilitated semi-pinacol rearrangement (Route B, Scheme 2.23).[11, 23] Substrates made by Brian Nderitu during his MChem project, previous Lee group members or the author are noted clearly in Scheme 2.23.[51]



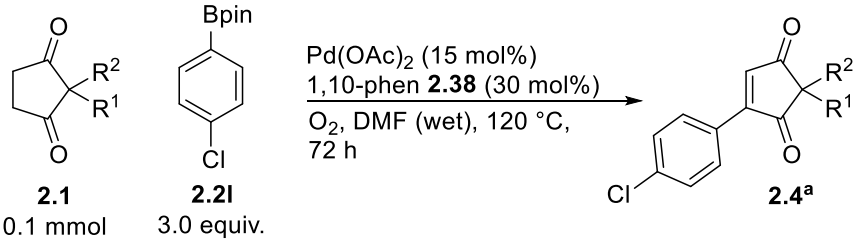
Scheme 2.23: General scheme for synthesis of 2,2-disubstituted cyclopentanediones **2.1**

2.5.2 2,2-Disubstituted Cyclopentanedione Scope

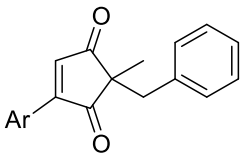
Next, we investigated the 2,2-disubstituted cyclopentanedione **2.1** scope with *p*-chlorophenyl Bpin **2.2l** and optimised conditions B (Table 2.6), this work was carried out in collaboration with MChem student, B. Nderitu.[‡51] The scope successfully shows that the reaction is tolerant of functionality such as an ester (**2.4gl** 67%) and oxidation

sensitive positions such as benzylic (**2.4al** 86%, **2.4bl** 79%) and benzyl protected alcohols (**2.4hl** 54%). Furthermore, spirocycles (**2.4il** 68%) and alkyl functionality (**2.4fl** 80%) dehydrogenate and couple in good yield. Aryl substituted substrates also proceeds through the ATC reaction without issue (**2.4cl** 75%, **2.4dl** 71%, **2.4el** 77%).

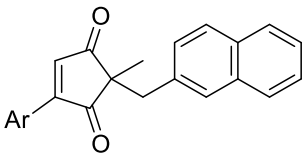
Table 2.6: 2,2-Disubstituted cyclopentanedione scope



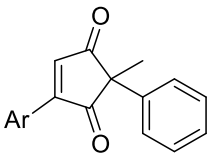
2.1 0.1 mmol | **2.2l** 3.0 equiv. | **2.4**[a]



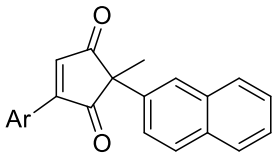
2.4al* 86%



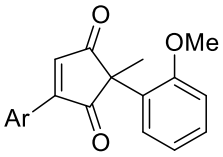
2.4bl‡ 79%



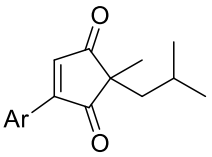
2.4cl‡ 75%



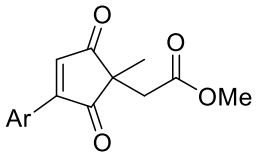
2.4dl* 71%



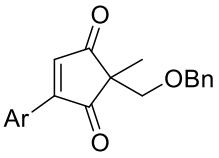
2.4el‡ 77%



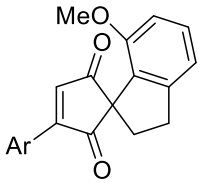
2.4fl‡ 80%



2.4gl‡ 67%



2.4hl* 54%



2.4il* 68%

[a] Isolated yield. ‡ Work completed by B. Nderitu. * Work completed by author.

2.6 Development of an ATC Reaction in Flow

2.6.1 Background

A batch ATC reaction was successfully optimised. Following this, it was decided that it would be interesting to investigate the ATC reaction under continuous flow conditions. Flow chemistry is becoming an increasingly powerful synthetic technique, and it has received lot of attention in recent times.[52, 53] It has been reported that it can result in better mixing of a reaction, improved heat transfer and can make the reaction easier and safer to scale up. The technique also allows for the increased control of several reaction parameters (such as temperature, pressure, flow rate), which can often result in improved reactivity and selectivity during a reaction.[53]

The ATC dehydrogenation/oxidative Heck reaction is an ideal candidate for development in continuous flow chemistry; the reasons for this are two-fold. First, the reaction is multiphasic (liquid-gas) and flow chemistry has been shown to improve phase mixing.[53] Secondly, both portions of this reaction, dehydrogenation[25] and oxidative Heck,[54] have been shown to work well separately under flow conditions but as of yet a combined ATC reaction of Pd(II)-catalysed aerobic dehydrogenation followed by oxidative Heck had not been studied in the literature. Therefore, we sought to develop this novel reaction under flow conditions.

The ATC reaction shown in Tables 2.5 and 2.6 is a multiphasic liquid-gas reaction. Often in these types of reactions under flow conditions, three types of flow regimes are observed: bubble, slug (segmented) and annular (Figure 2.2). The regime observed is dictated by the diameter of the tubing used, flow rate of the gas in the system and viscosities of the other reactants present. The most commonly observed is the segmented flow, which was observed during our studies. The segmented flow significantly

increases the contact interface between the gas and the reaction mixture with respect to carrying the reaction out in a round bottom flask. For example, the interfacial surface area in a 5 mL round bottom flask verses a gas-liquid microchannel flow reactor is 141 v. 3400-18000 m^2m^{-3}.[52] Therefore, segmented flow allows for more efficient phase transfer between a gas and a liquid.

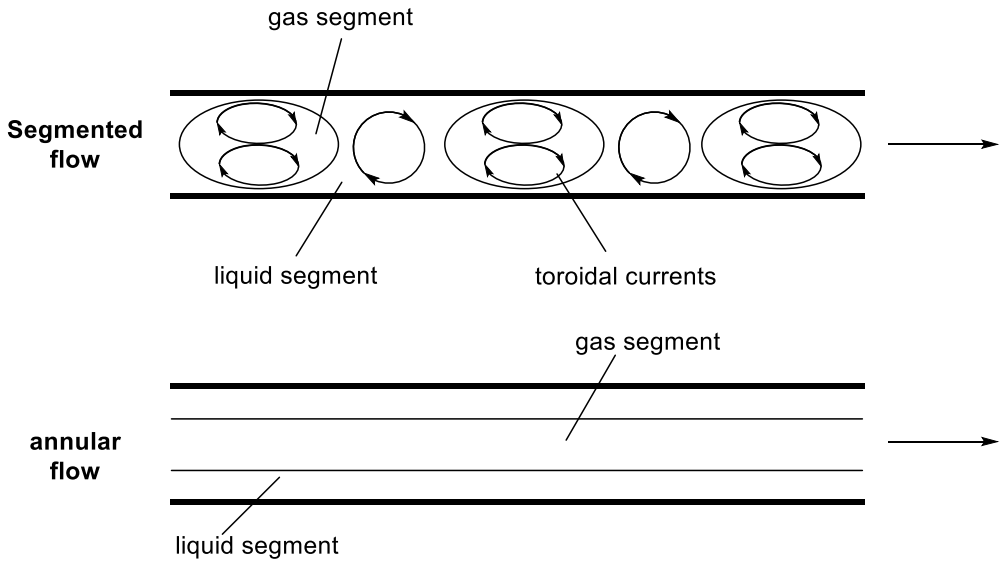


Figure 2.2: Recreated from Baxendale *et al*.[52]
Visualisation of segmented flow versus annular flow.

Our aim was to develop a one-pot dehydrogenation/oxidative Heck reaction procedure in flow. If successful, this would be the first instance of a Pd(II)-catalysed aerobic ATC dehydrogenation then subsequent oxidative Heck reaction being performed in continuous flow. Furthermore, we also envisaged a scale up of the ATC reaction would be easier and safer if performed in continuous flow especially with the use of molecular oxygen at elevated temperatures.

We planned to carry out all the continuous flow ATC reactions in a commercial Vapourtec continuous flow reactor. The Vapourtec reactor has options to alter flow rates through each pump independently, and peristaltic pumps, so liquid, gas and small particulates are suitable. The reaction mixture would pass through pump A and

molecular oxygen would pass through pump B, meet at a T-junction and then form the important segmented flow before passing through the heated reactor coil and cycled back to the round bottom flask to start the process again (Figure 2.3).

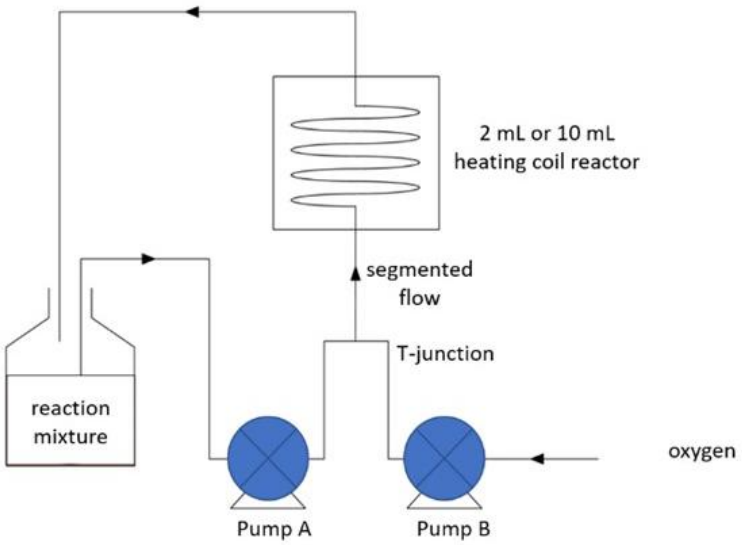


Figure 2.3: Vapourtec continuous flow reactor set up

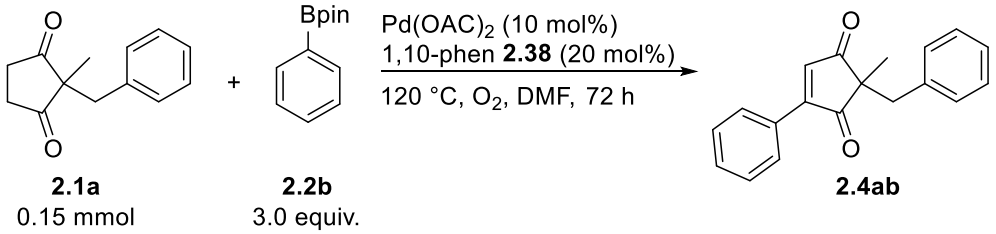
2.6.2 Optimisation of Continuous Flow Conditions with Phenyl Pinacol Boronic Ester

Initially, we started with optimised batch conditions for the coupling of benzyl substituted cyclopentanedione **2.1a** and phenyl pinacol boronic ester **2.2b** (Table 2.7)**.** The flow reactor used was 2 mL in volume, however, in order to get efficient cycling through the system we needed to use a reaction volume of at least 3 mL. Thankfully, as we were passing a gas through the flow reactor (oxygen), we were able to half the reaction volume required. This meant that we did not need to change the concentration from the batch reaction and only needed to scale the reaction up slightly to 0.15 mmol in 1.5 mL solvent.

There were several parameters we could alter with flow chemistry, and it was decided to only alter flow parameters as opposed to the stoichiometry of the reaction to get more

of an understanding. For simplicity, the flow rate of the reaction and that of the gas were kept the same and the reactor temperature was maintained at 120 °C, in line with optimised batch conditions.

Table 2.7: Initial flow chemistry optimisation studies



Entry[a]	Flow rate (mL min^{-1})		Residency time	Yield (%)[b]		
	Reaction	O_2	(min)	2.4ab	2.3a	2.1a
1	0.1	0.1	10	33	35	Trace
2	0.4	0.4	2.5	45[c]	20%[c]	-
3	0.6	0.6	1.7	35	29	-

[a] 2 mL reactor volume. [b] Yield determined by ^{1}H NMR spectroscopy by comparison to internal standard 1,3,5-trimethoxybenzene. [c] Isolated yield.

A flow rate of 0.1 mL min^{-1} (Table 2.17, entry 1, residency time 10 min), resulted in complete conversion of dione starting material **2.1a** to enedione **2.3a** but incomplete conversion to the oxidative Heck coupled product **2.4ab** within 72 h cycling. Increasing the flow rate to 0.4 mL min^{-1} (entry 2, residency time 2.5 min) furnished the coupled product **2.4ab** in 45% isolated yield. However, a flow rate of 0.6 mL min^{-1} (entry 3, residency time 1.67 min) resulted in a decrease in yield.

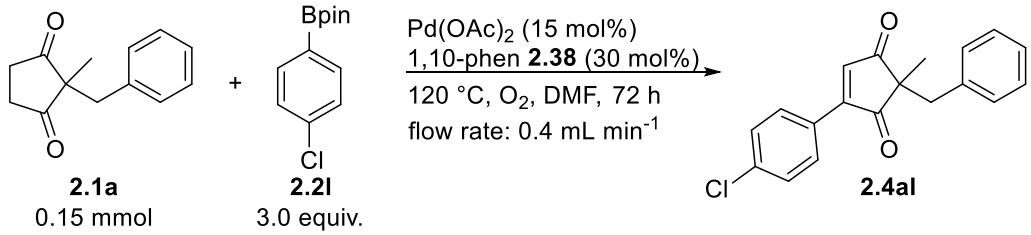
Issues arose when we tried to carry out the reaction at 150 °C . As O_2 was being fed through the reactor at the same time, this made controlling back pressure applied to the continuous flow reaction difficult. Back pressure is required at this increased temperature to stop the DMF solvent flashing through the lines, making the true flow rate and therefore the residency time difficult to estimate. As a result, several leaks in

the continuous flow equipment occurred and so we abandoned carrying out the reaction at temperatures above 120 °C

2.6.3 Studies with *p*-Chlorophenyl Pinacol Boronic Ester

Next, we tried the optimised conditions for *p*-chlorophenyl Bpin **2.2l** with benzyl substituted enedione **2.1a,** using $Pd(OAc)_2$ (15 mol%) as catalyst and 1,10-phen **2.38** (30 mol%) as ligand (Table 2.8). Under these conditions we were able to push the reaction almost to completion with no dione starting material **2.1a**, 6% enedione **2.3a** still present and an NMR yield of 55% of coupled product **2.4al** (entry 1). This yield is still much lower than is observed in batch (86% yield batch *vs.* 55% yield flow), and strangely, analysis of the crude mixture by ^{1}H NMR spectroscopy indicated a clean conversion. The flow instrument and all the lines were washed several times and analysed by ^{1}H NMR spectroscopy, but the washings were also clean. No leaks could be detected in the instrument either to account for such a decrease in yield. We tried to push the reaction by increasing the concentration to 0.15 mol L^{-1}; all starting material and enedione were then consumed. The isolated yield was comparable to the ^{1}H NMR yield of the lower concentration (entry 2, 53%). However, without a clear reason as to why the yield is lower with respect to batch, this was accepted as the best result of the flow investigations.

Table 2.8: Investigations with *p*-chlorophenyl pinacolboronic ester **2.2l** in continuous flow



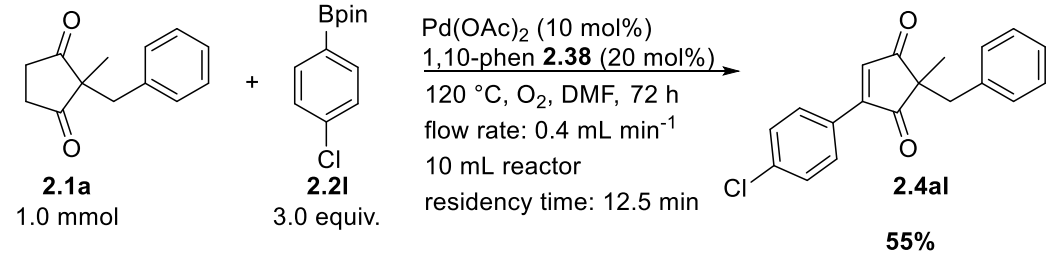
2.1a 0.15 mmol + **2.2l** 3.0 equiv. → **2.4al**

Entry[a]	Concentration (mol/L)	Yield (%)[b]		
		2.1a	**2.3a**	**2.4al**
1	0.1	-	6[e]	55[e]
2	0.15	-	trace	53

[a] Reactor volume 2 mL. [b] Isolated yield. [e] Yield determined by ^{1}H NMR spectroscopy by comparison to internal standard 1,3,5-trimethoxybenzene.

2.6.4 Scale-up Under Continuous Flow Conditions – Proof of Principle

With optimised small-scale flow conditions in hand, we turned our attention to carrying out a continuous flow scale up as proof of principle. Scaling up a reaction using a gas as a reagent is quite difficult, due to a decrease in surface area of the gas-liquid interface.[52] There was not a dramatic difference in yield between 0.1 mol L^{-1} *verses* 0.15 mol L^{-1} (Table 2.8) so we decided to maintain the concentration at 0.1 mol L^{-1}.



2.1a 1.0 mmol + **2.2l** 3.0 equiv. → **2.4al** **55%**

Scheme 2.24: Scale up under continuous flow conditions

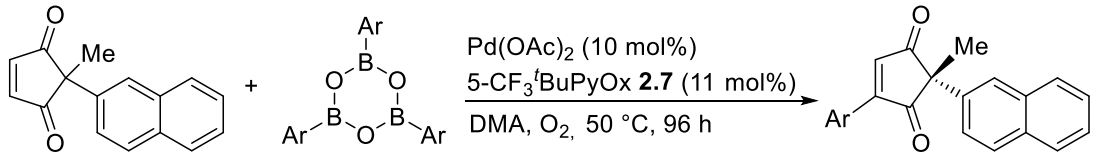
The reaction was scaled up from 0.15 mmol to 1.0 mmol under continuous flow conditions as proof-of-principle (Scheme 2.24) in a 10 mL reactor. The reaction was

scaled up directly to maintain a concentration of 0.1 mol L^{-1} and, pleasingly, by TLC the reaction appeared to go to completion. Unlike the batch reaction for the synthesis of coupled product **2.4al**, the phenol side-product associated with the use of *p*-chlorophenyl pinacol boronic ester **2.2l** became an issue during purification, but this was easily removed using carbonate on a polymer support. The coupled product **2.4al** was successfully isolated in 55% yield, where the 1.0 mmol scale and 0.15 mmol scale yields in continuous flow are comparable (Table 2.8, entry 1 *vs*. Scheme 2.24).

2.7 Enantioselective Studies – Proof of Principal

2.7.1 Introduction

The final aim of this project was to develop an enantioselective ATC desymmetrisation reaction of 2,2-disubstituted cyclopentanediones **2.1**. As a point of comparison, we aimed to replicate the enantiomeric ratio of a desymmetrised product reported in the original 2015 paper[12] with this new ATC methodology. The results we aimed to replicate were the enantioselective oxidative Heck coupling of naphthyl-substituted cyclopentenedione **2.3d** with *p*-methoxyphenyl boroxine **2.5a** (90:10 e.r.) and *p*-chlorophenyl boroxine **2.5l** (94:6 e.r.) (Scheme 2.25).



2.1d

2.5a Ar = *p*-$MeOC_6H_4$-
2.5l Ar = *p*-ClC_6H_4-

2.4da 100%, 90:10 e.r.
2.4dl 85%, 94:6 e.r.

Scheme 2.25: Aim to replicate results with ATC desymmetrisation protocol[12]

2.7.2 Dehydrogenation Optimisation

In order to achieve an enantioselective ATC dehydrogenation/oxidative Heck reaction, the dehydrogenation reaction would have to be performed with a chiral catalyst to ensure the enantiomeric ratio of the second oxidative Heck step would not be affected, since both reactions will be conducted in one-pot. Therefore, we set out to re-optimise the dehydrogenation reaction with chiral ligands, choosing to focus on *N*,*N*-type pyridine oxazoline ligands ((*S*)-PyOx) (Figure 2.4). Primarily these were selected because *N*,*N*-type ligands are stable to air and moisture[55] and they were shown to be successful in carrying out the enantioselective oxidative Heck reactions (see Chapter 1, Section 1.3 for further details) and the oxidative Heck desymmetrisation in our previous work.[12]

The racemic optimisation was extensively carried out using benzyl substituted cyclopentanedione **2.1a** and, for consistency, the initial dehydrogenation with a chiral ligand was carried out using this substrate. Similarly, with the racemic optimisation, we were not interested in isolating the enedione intermediate **2.3a** so the main concern was pushing the dehydrogenation reaction to full conversion. This was determined by ^{1}H NMR analysis of the crude reaction mixture unless otherwise stated.

Utilising the previously optimised dehydrogenation conditions as a starting point, a chiral ligand screen was carried out (Table 2.9). The (*S*)-PyOx ligands (Figure 2.4) were not as conducive to the dehydrogenation reaction as 1,10-phenanthroline type ligands. Initially performing the reaction for 24 h, conversions were poor for all three (*S*)-PyOx ligands studied (Table 2.9). Increasing the reaction time to 48 h was helpful for conversions, with a promising conversion of 75% achieved with 4-CF_3-^{t}BuPyOx **2.8**. However, only 15 mol% ligand was used for the dehydrogenation with ^{t}BuPyOx **2.6,**

which may explain the poorer conversion with respect to the other two (*S*)-PyOx ligands trialled.

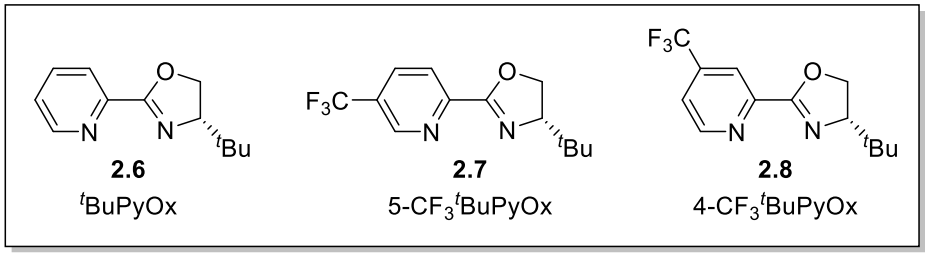
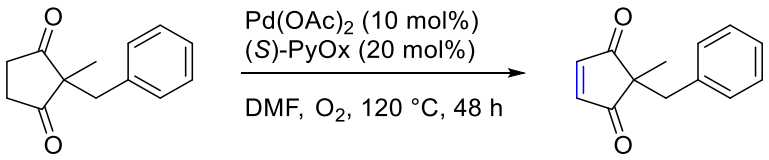


Figure 2.4: Structure of chiral (*S*)-PyOx ligands

Table 2.9: Initial dehydrogenation optimisation with chiral ligand and substrate **2.1a**



2.1a
0.1 mmol

2.3a

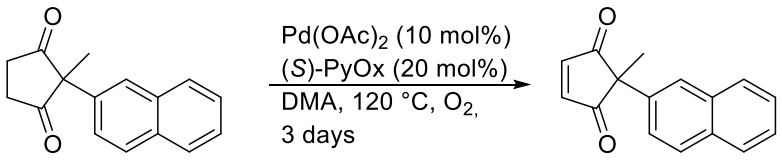
Entry	(*S*)-PyOx	Conversion (%)[b]	
		24 h	**48 h**
1[a]	^{t}BuPyOx **2.6**	40	43
2	5-CF$_3$^{t}BuPyOx **2.7**	41	53
3	4-CF$_3$^{t}BuPyOx **2.8**	53	75

[a] 15 mol% (*S*)-PyOx. [b] %Conversion calculated through analysis of ^{1}H NMR spectra

These positive initial optimisation reaction conditions were carried forward to attempt the dehydrogenation of cyclopentanedione **2.1d** that we were interested in for the enantioselective studies. A few alterations were made to the conditions, the reaction time was increased to 72 h and the solvent was changed to the less ligating dimethyl acetamide (DMA), as this solvent improved the enantiomeric ratio of the oxidative Heck reaction in the original desymmetrisation work.[12] These changes made a significant

difference in the reaction over all three (*S*)-PyOx ligands, producing %conversions which were high enough to move on to the one-pot reaction optimisation (Table 2.10).

Table 2.10: Dehydrogenation optimisation with cyclopentanedione **2.1d**



2.1d
0.1 mmol

2.3d

Entry	(*S*)-PyOx	Conversion (%)[a]
1	^{t}BuPyOx **2.6**	87%
2	5-CF$_3$^{t}BuPyOx **2.7**	92%
3	4-CF$_3$^{t}BuPyOx **2.8**	100 (78%)[b]

[a] %Conversion determined by ^{1}H NMR analysis. [b] Isolated yield

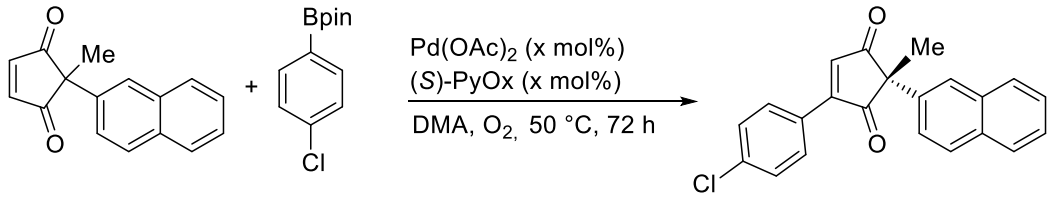
2.7.3 Investigations into an Enantioselective ATC Reaction

2.7.3.1 Enantioselective oxidative Heck coupling with *p*-chlorophenyl pinacol boronic ester 2.2l

Use of a pinacol boronic ester **2.2** was established as key for the racemic reaction (see Section 2.3.3). However, when we tried to carry out an enantioselective oxidative Heck reaction with naphthyl-substituted cyclopentenedione **2.3d** and *p*-chlorophenyl Bpin **2.2l** with (*S*)-PyOx ligands, no reaction was observed (Table 2.11). The reaction temperature was reduced to 50 °C, in line with the original work, to achieve good enantioselectivity.[12] Applying the optimised dehydrogenation conditions with chiral ligand 4-CF$_3$^{t}BuPyOx **2.8** at 50 °C only returned 93% starting material **2.1d** (entry 1). Even increasing catalyst and ligand loading through portionwise addition was not enough to force any coupling. It was decided that the reaction temperatures required for

good enantioselectivity in the previous work, would render pinacol boronic esters **2.2** too unreactive for the oxidative Heck coupling reaction. Therefore, another boron coupling species would need to be selected, so we opted to return to using aryl boroxines.

Table 2.11: Oxidative Heck desymmetrisation reaction with *p*-chlorophenyl Bpin **2.2l**



2.3d 0.1 mmol | **2.2l** 2.5 equiv. | **2.4dl**

Entry	Catalyst loading (mol%)	(*S*)-PyOx	(*S*)-PyOx loading (mol%)	Result
1	10	4-CF_3^{t}BuPyOx **2.8**	20	No reaction[a]
2[b]	3 × 5 mol%	4-CF_3^{t}BuPyOx **2.8**	3 × 6 mol%	No reaction
3[b]	3 × 5 mol%	^{t}BuPyOx **2.6**	3 × 6 mol%	No reaction
4[b]	3 × 5 mol%	5-CF_3^{t}BuPyOx **2.7**	3 × 6 mol%	No reaction

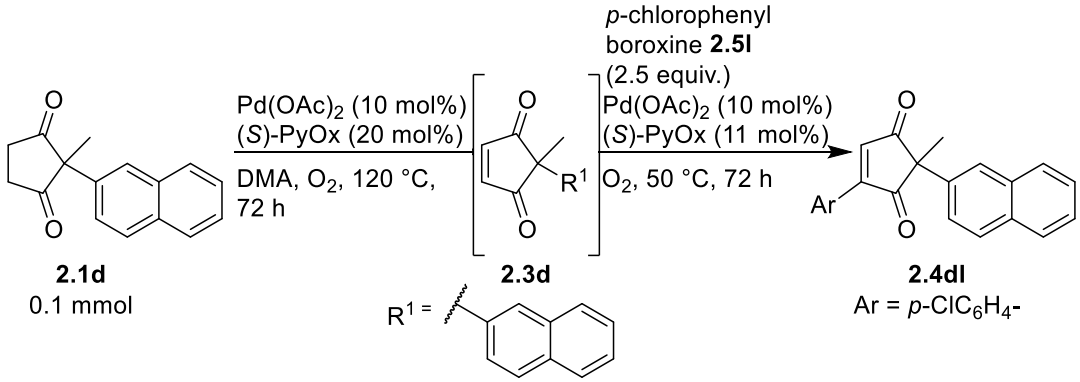
[a] 93% Isolated yield of starting material. [b] Catalyst and ligand were added in 3 portions total. First portion at start then another portion after 24 h, then after 48 h and left to stir for another 24 h.

2.7.3.2 Enantioselective ATC reaction with *p*-chlorophenyl boroxine 2.5l

Pleasingly, carrying out the dehydrogenation reaction on naphthyl-substituted cyclopentanedione **2.1d** and then adding boroxine **2.5l** after completion of the first step successfully formed the oxidative Heck coupled product (Table 2.12). Although 4-CF_3^{t}BuPyOx **2.8** gave the best %conversion during the dehydrogenation reaction optimisation, all (*S*)-PyOx ligands gave a high enough conversion to enedione **2.3d** to warrant being trialled in the enantioselective ATC reaction. ^{t}BuPyOx **2.6** (50% yield,

62:38 e.r.) and 5-CF_3^{t}BuPyOx **2.7** (49% yield, 64:36 e.r.) gave the best yield of oxidative Heck product **2.4dl**, whereas 4-CF_3^{t}BuPyOx **2.8** furnished **2.4dl** in 43% yield and only 53:41 e.r.

Table 2.12: Enantioselective ATC reaction with *p*-chlorophenyl boroxine **2.5l**



Entry[a]	(*S*)-PyOx	Yield (%)[b]	e.r.[c]
1	^{t}BuPyOx **2.6**	50	62:38
2	5-CF_3^{t}BuPyOx **2.7**	49	64:36
3	4-CF_3^{t}BuPyOx **2.8**	41	53:41

[a] Corresponding boronic acid from bottle dehydrated in a separate flask under vacuum with a heat gun until all visible condensation was driven off and **2.5l** weighed out quickly in air. [b] Isolated yield. [c] E.r. determined by CSP-HPLC.

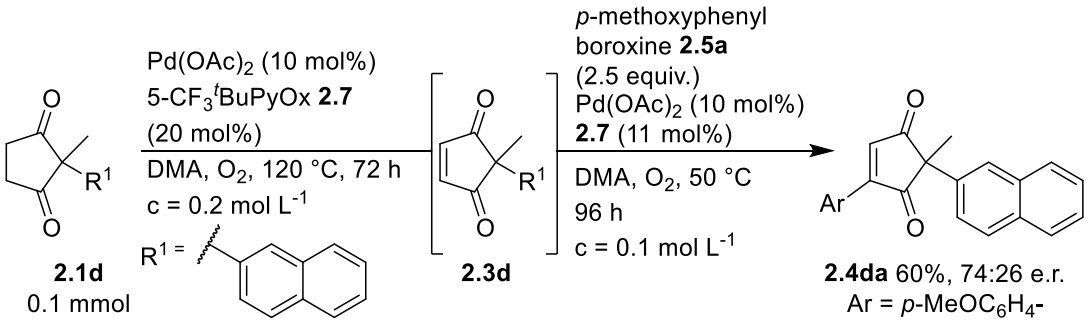
Although carrying out the enantioselective ATC reaction was for proof of principle, the enantioselectivity of the ATC reaction was lower than we initially anticipated. The reaction temperature of the coupling reaction could not be lowered any further to improve e.r. as the reaction time was already excessively long at 144 h. Furthermore, the yield was nearly half of what was previously reported. (Table 2.12, entry 2, 50% vs. Scheme 2.25, **2.4dl** 85%).

In our aim to develop an enantioselective dehydrogenation/oxidative Heck ATC reaction, we succeeded. However, in the aim to match the yield and enantiomeric ratio, we did not: both are lower than was originally reported in the 2015 oxidative Heck

paper.[12] These results suggest a Pd(II)-catalysed aerobic dehydrogenation/oxidative Heck desymmetrisation may not be applicable to synthesising highly enantioenriched products, which was a disappointing conclusion. Although frustrating, we proceeded with trying to replicate the other desymmetrisation result we selected, **2.4da** (Scheme 2.25).

2.7.3.3 Enantioselective ATC reaction with *p*-methoxyphenyl boroxine 2.5a

In the hope that the poor yield and enantioselectivity was due to the sluggish performance of an electron-withdrawing aryl boroxine **2.5l**, we turned our attentions to trying to reproduce the original result from the coupling of **2.3d** with *p*-methoxyphenyl boroxine **2.5a** (Scheme 2.25). Carrying forward the best result from the ATC reactions with *p*-chlorophenyl boroxine **2.5l**, it was decided that we should focus on the use of 5-CF_3-^{t}BuPyOx **2.7**. Pleasingly, applying the best conditions established in Table 2.12 furnished the dehydrogenation/coupled product **2.4da** in 60% yield and 74:26 e.r. (Scheme 2.26). However, the yield and especially the e.r. are not as high as was reported for the separate 2-step reaction.[12]

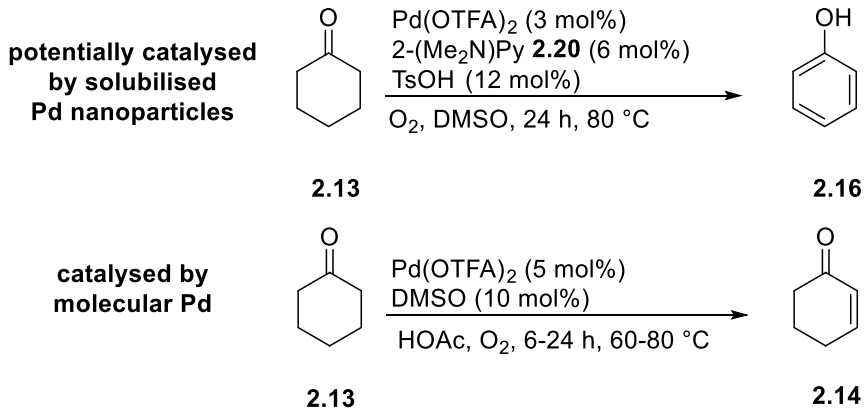


Scheme 2.26: One-pot ATC reaction with *p*-methoxyphenyl boroxine **2.5a**

2.7.3.4 Rational for poor enantioselectivity observed during ATC desymmetrisation reactions

Frustratingly, the enantiomeric ratios observed during the ATC enantioselective dehydrogenation/oxidative Heck reactions were poor (Table 2.12, Scheme 2.26), and not comparable with previous 2-separate step results in the Lee group.[12] The enantioselectivities observed for the oxidative Heck coupling reaction alone with *p*-methoxyphenyl boroxine **2.5a** and enedione **2.3d** were acceptable. This reaction gave 95:5 e.r. and 97% isolated yield of **2.4da**. We hypothesised that an explanation for the reduced observed e.r. must lie with the new component to the reaction: the Pd(II)-catalysed aerobic dehydrogenation.

Upon closer inspection of the literature, it was discovered that, as the dehydrogenation reaction is carried out at an elevated temperature of 120 °C, the palladium(II) catalyst may not be a discrete molecular species [$Pd(OAc)_2$/ligand] for the whole duration of the reaction. The catalyst may change to form solubilised nanoparticles which could also catalyse the reaction.[56] Stahl *et al.* carried out further mechanistic studies into his 2011 work on the $Pd(TFA)_2$ catalysed dehydrogenation reaction of cyclohexanone **2.13** to phenol **2.16** with 2-(Me_2N)pyridine **2.20** as ligand (Scheme 2.27). There were several compelling pieces of qualitative and kinetic evidence to suggest the presence of solubilized palladium nanoparticles and their role in the catalysis of the dehydrogenation reaction. Conversely, they also investigated the $Pd(TFA)_2$DMSO catalyst system which chemoselectively dehydrogenates cyclohexanone **2.13** to cyclohexanone **2.14**, which showed no such evidence for the presence of Pd-nanoparticles. They suggest DMSO is provided stability to the molecular Pd catalyst and retarding the formation of palladium black (Scheme 2.27).



Scheme 2.27: Stahl's proposed reactions catalysed by solubilised Pd nanoparticles[38] or a molecular Pd catalyst[25, 56]

The catalyst systems being utilised throughout our ATC studies are much closer in nature to the catalyst system used in Stahl *et al*.'s dehydrogenation to phenol **2.16** work, which exhibited evidence for the presence of Pd nanoparticle. Both reactions employ pyridine type ligands. Although no reactions were ever carried out to confirm the presence of nanoparticles in our ATC reaction mixture, several qualitative indicators were observed during the dehydrogenation portion of the reaction. For example, palladium black/mirror deposits on the side of the reaction flask or a dark red/brown reaction mixture can indicate the presence of non-molecular Pd species, both of which were observed during our investigations. Furthermore, the use of high dielectric constant solvents can also promote the formation of metallic nanoparticles (DMF ε = 36.7, DMA ε = 37.6).[57, 58]

This information shed light on the possible reasons for the decreased enantiomeric ratio observed in the ATC reaction. If soluble nanoparticles are formed in the reaction mixture, even though an additional portion of catalyst and ligand are added to the reaction during the oxidative Heck stage and the reaction temperature is decreased, the initial presence of nanoparticles could promote further formation of nanoparticles or they may catalyse the oxidative Heck reaction themselves. Both options would result in

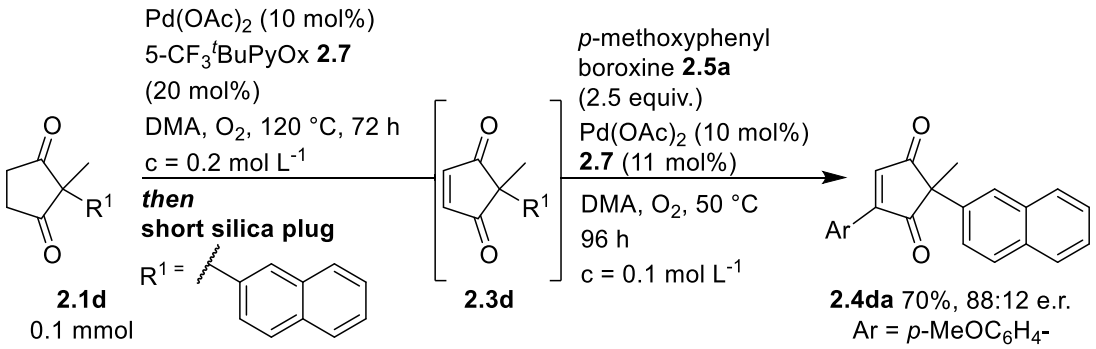
a decrease in the enantioselectivity of the reaction. Unfortunately, this suggests that the enantiomeric ratios that are furnished during the ATC oxidative Heck desymmetrisation reaction are unlikely to improve.

2.7.4 Investigations into an Enantioselective Telescoped Reaction

In light of the realisation that the enantiomeric ratios of the ATC reaction were unlikely to improve, we decided to investigate a *telescoped* approach to the enantioselective reaction. A benefit of carrying out reactions in one-pot is the reduction in the number of purifications which need to be carried out between each step. The synthesis of cyclopentanedione **2.1** and then formation of the cyclopentenedione **2.3** by $CuBr_2$ dehydrogenation, requires at least two full formal purifications. This uses large volumes of solvent, silica and (wo)man hours depending on the complexity of the separation. If an enantioselective Pd(II)-catalysed *telescoped* dehydrogenation/oxidative Heck reaction could be developed, this would negate the need for one of the columns in the synthesis of desymmetrised cyclopentenedione product **2.4** without sacrificing good enantiomeric selectivity.

We opted to trial the enantioselective telescoped synthesis of **2.4da** as it was the most promising enantioselective ATC reaction in terms of e.r. and yield. The first step of the telescoped reaction was carried out similarly to the ATC reaction, with increased concentration during the dehydrogenation step and using 5-CF_3-^{t}BuPyOx **2.7**. Instead of immediately dropping the reaction temperature and adding the boroxine **2.5a** for the oxidative Heck reaction, we filtered the dehydrogenation reaction mixture through a short silica plug (in a Pasteur pipette) to remove any potential Pd nanoparticle contaminants (a black band was observed at the top surface of the silica plug). The reaction mixture was then concentrated, and the remaining reagents and solvent were added to carry out the oxidative Heck reaction. To our delight, this furnished the

dehydrogenation oxidative Heck desymmetrised product **2.4da** in 70% yield and 88:12 e.r. (Scheme 2.28), within experimental error of the original e.r. (original e.r. 90:10, Scheme 2.25).



Scheme 2.28: Telescoped approach to the dehydrogenation/oxidative Heck desymmetrisation of **2.1d**

In order to establish whether the chiral molecular Pd(II) catalyst comes through the silica plug after the dehydrogenation reaction, ^{1}H NMR studies were carried out. A solution containing a 1:2 mixture of $Pd(OAc)_2$/5-CF_3^{t}BuPyOx **2.7** was analysed by ^{1}H NMR spectroscopy before and after filtration through a short silica plug. The results show that the ligated $Pd(OAc)_2$/5-CF_3^{t}BuPyOx **2.7** complex does not come through the silica plug but unligated 5-CF_3^{t}BuPyOx **2.7** ligand does. This evidence suggests that the same chiral ligand is necessary for the dehydrogenation step to get good enantioselectivity in the second oxidative Heck step, and that an achiral ligand cannot be used for the dehydrogenation step.

Another telescoped reaction was performed where no additional $Pd(OAc)_2$ or 5-CF_3^{t}BuPyOx **2.7** was added after the dehydrogenation step and the silica plug filtration. Only 63% ^{1}H NMR yield (by ^{1}H NMR analysis) of enedione **2.3d** was observed with no oxidative Heck coupling. This control reaction confirms the need for additional catalyst and ligand addition for successful oxidative Heck.

2.8 Conclusions

In conclusion, a new Pd(II)-catalysed dehydrogenation reaction has been successfully developed, along with its incorporation into a racemic auto-tandem catalytic dehydrogenation/oxidative Heck coupling reaction of 2,2-disubstituted cyclopentanediones **2.1** and aryl pinacol boronic esters **2.2**. The racemic reaction allowed for a broad scope of substituted cyclopentanediones **2.1** and aryl Bpins **2.2** to be successfully coupled, with even *p*-bromophenyl Bpin **2.2c** reacted well without any evidence of oxidative addition at the Br–C bond. The first example of Pd(II)-catalysed aerobic dehydrogenation/oxidative Heck reaction was also successfully investigated in continuous flow, including the study of a scale up of this multiphasic ATC reaction. Finally, the first Pd(II)-catalysed auto-tandem catalytic aerobic dehydrogenation/oxidative Heck desymmetrisation reaction was investigated, and although the result was not as originally envisaged, it was interesting, nonetheless. A telescoped enantioselective approach was investigated which provides proof of principle that a full formal purification is not required between the dehydrogenation and oxidative Heck steps.

2.9 Experimental Data

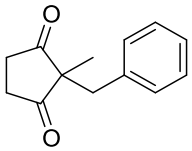
2.9.1 General Experimental Considerations

^{1}H NMR spectra were recorded on Bruker AV 300 and AV 400 spectrometers at 300 and 400 MHz respectively and referenced to residual solvent. ^{13}C NMR spectrum were recorded using the same spectrometers at 75 and 100 MHz respectively. Chemical shifts (δ in ppm) were referenced to tetramethylsilane (TMS) or to residual solvent peaks ($CDCl_3$ at δ_H 7.26 or δ_C 77.16 ppm). *J* values are given in Hz and s, d, dd, t, q, p and m abbreviations correspond to singlet, doublet, doublet of doublet, triplet, quartet, pentet and multiplet. Mass spectra were obtained at the EPSRC National Mass Spectrometry Service Centre in Swansea. Infrared spectra were obtained on Perkin-Elmer Spectrum 100 FT-IR Universal ATR Sampling Accessory, deposited neat or as a chloroform solution to a diamond/ZnSe plate.

Flash column chromatography was carried out using Matrix silica gel 60 from Fisher Chemicals or Flurochem and TLC was performed using Merck silica gel 60 F254 precoated sheets and visualised by UV (254 nm) or stained by the use of aqueous acidic $KMnO_4$ or aqueous acidic ammonium molybdate as appropriate. DMF was obtained dry from a solvent purification system or purchased from Sigma Aldrich without further purification. All aryl boronic acids or pinacol boronic esters were purchased from Sigma-Aldrich or Fluorochem. Unless otherwise stated, where petroleum ether is used in procedures, petroleum ether 40-60 °C is the solvent used. All one-pot reactions were run under an O_2 atmosphere provided by a balloon filled with O_2 supplied by BOC. Continuous flow chemistry was performed on a Vaportec flow instrument with a 2 or 10 mL volume reactor coil.

2.9.2 Synthesis of Starting Materials

2-Benzyl-2-methylcyclopentane-1,3-dione 2.1a[11]

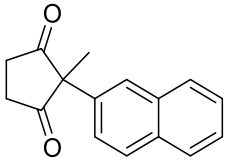


2.1a

2-Methycyclopentane-1,3-dione **2.9** (2.0086 g, 17.91 mmol, 1 equiv.) was added to anhydrous CH_3CN (100 mL) before DBU (3.2 mL, 21.41 mmol, 1.2 equiv.) was added dropwise at 0 °C. The solution was warmed to room temperature and stirred for 30 minutes. Benzyl bromide **2.10a** (4.2 mL, 35.68 mmol, 2 equiv.) was added dropwise and the reaction mixture heated at reflux for 23 h. The reaction mixture was quenched with H_2O and the aqueous layer was washed with EtOAc until the organic layer was colourless. The combined organic layers were dried over $MgSO_4$ before solvent was removed under reduced pressure. The resulting residue was purified by silica gel column chromatography (petroleum ether/EtOAc 5:1) to yield **2.1a** (2.7683 g, 13.69 mmol, 76%) as a pale yellow crystalline solid.

Mp: 53-54 °C (petroleum ether/EtOAc) (literature mp: 50-52 °C);[11] R_f: 0.28 in 5:1 petroleum ether:EtOAc; ν_{max}/ cm^{-1}: 3028, 2979, 2925, 1755, 1715, 1453, 1438, 1410, 1372, 1326, 1199, 1078, 995, 789, 758, 705; ^1H NMR (300 MHz, $CDCl_3$) δ 7.24 – 7.18 (m, 3H, Ar-H), 7.03 (m, 2H, Ar-H), 2.96 (s, 2H, CH_2Ph), 2.48 (ddd, *J* = 18.9, 7.0, 0.9 Hz, 2H), 1.98 (ddd, *J* = 18.9, 7.0, 0.9 Hz, 2H), 2.60 – 2.48 (m, 1H, CH_2), 2.11 – 1.99 (m, 1H, CH_2), 1.20 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 217.5 (C), 135.9 (C), 129.7 (CH), 128.7 (CH), 127.4 (CH), 58.4 (C), 43.2 (CH_2), 35.9 (CH_2), 20.1 (CH_3).

2-Methyl-2-(naphthalen-2-yl)cyclopentane-1,3-dione 2.1d[11]

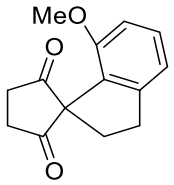


2.1d

2-Acetonaphthone **2.11d** (0.9939 g, 5.84 mmol, 1.0 equiv.) and 1,2-bis(trimethylsiloxy)cyclobutene **2.12** (2.3 mL, 8.85 mmol, 1.5 equiv.) were added to dichloromethane (10 mL), followed by drop-wise addition of $BF_3.OEt_2$ (1.1 mL, 8.85 mmol, 1.5 equiv.) at 0 °C. The solution was warmed to room temperature bath for 24 h under an inert atmosphere. Water (10 mL) was added and the reaction left to stir for 1 h. The organic layer was separated, and the aqueous layer was washed with dichloromethane (2 × 10 mL). The combined organic layer was washed with brine, dried over $MgSO_4$ and the solvent removed under reduced pressure. The residue was purified by silica gel column chromatography (10:1 hexane:EtOAc) to yield **2.1d** (0.645 g, 2.7 mmol, 46%) as a pale yellow oil.

R_f: 0.2 in 5:1 petroleum ether:EtOAc; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 – 7.76 (m, 3H, Ar-H), 7.62 (d, *J* = 2.0 Hz, 1H, Ar-H), 7.53 – 7.46 (m, 2H, Ar-H), 7.37 (dd, *J* = 8.7, 2.0 Hz, 1H, Ar-H), 3.01 – 2.71 (m, 4H, CH_2CH_2), 1.52 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.2 (C), 134.4 (C), 133.5 (C), 132.8 (C), 129.6 (CH), 128.2 (CH), 127.7 (CH), 126.9 (CH), 126.8 (CH), 125.8 (CH), 123.9 (CH), 62.5 (C), 35.5 (CH_2), 19.9 (CH_3); HRMS (TOF MS ASAP) *m/z* calc. for $C_{16}H_{15}O_2$: 239.1072 $[M+H]^+$ found: 239.1070.

7'-Methoxy-2',3'-dihydrospiro[cyclopentane-1,1'-indene]-2,5-dione 2.1i[12]



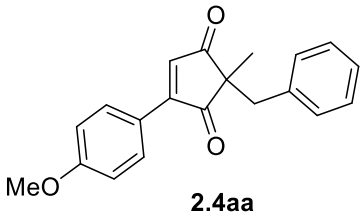
2.1i

7-Methoxy-2,3-dihydro-1H-inden-1-one **2.11i** (200.1 mg, 1.23mmol, 1.0 equiv.) was added to dichloromethane (15 mL) and cooled to -78 °C. $BF_3.OEt_2$ (0.3 mL, 2.46 mmol, 2.0 equiv.) was added drop-wise and the reaction was stirred for 45 minutes at -78 °C. 1,2-Bis(trimethylsiloxy)cyclobutene **2.12** (475 µL, 1.85 mmol, 1.5 equiv.) was added before the reaction was allowed to warm to room temperature and stirred for a further 24 h. Water (8 mL) was added and the reaction left to stir for 30 min. The organic layer was separated, and the aqueous layer was washed with dichloromethane (2 × 10 mL). The combined organic layer was washed with brine, dried over $MgSO_4$ and the solvent removed under reduced pressure. The residue was purified by silica gel column chromatography (5:1 → 1:1 hexane:EtOAc) to yield **2.1i** (91.1 g, 0.32 mmol, 32%) as a pale yellow solid.

M.p 102-103 °C (hexane/$CHCl_3$) (literature: 104-105 °C)[12]; R_f: 0.4 in 2:1 petroleum ether:EtOAc; ν_{max}/ cm^{-1}: 2938, 2840, 1716, 1601, 1586, 1478, 1455, 1269, 1074, 777;^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (dd, *J* = 8.1, 7.6 Hz, 1H, Ar-H), 6.89 (dd, *J* = 7.6, 0.9 Hz, 1H, Ar-H), 6.62 (dd, *J* = 8.1, 0.9 Hz, 1H, Ar-H), 3.72 (s, 3H, OCH_3), 3.18 (t, *J* = 7.3, Hz, 2H, CH_2), 3.10 – 2.93 (m, 2H, CH_2), 2.93 – 2.76 (m, 2H, CH_2), 2.38 – 2.28 (m, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.9 (C), 154.3 (C), 147.8 (C), 130.4 (C), 130.4 (CH), 117.7 (CH), 108.6 (CH), 66.1 (C), 55.5 (CH_3), 36.6 (CH_2), 35.6 (CH_2), 32.6 (CH_2).

2.9.3 Pinacol Boronic Ester Scope

2-Benzyl-4-(4-methoxyphenyl)-2-methylcyclopent-4-ene-1,3-dione 2.4aa[12]

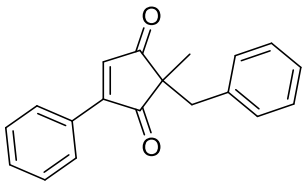


2.4aa

Conditions B: 2-Benzyl-2-methylcyclopentane-1,3-dione **2.1a** (20.4 mg, 0.101 mmol, 1.0 equiv.), 1,10-phenanthroline **2.38** (5.4 mg, 29.97 μmol, 0.3 equiv.), $Pd(OAc)_2$ (3.4 mg, 15.14 μmol, .15 equiv.) and 2-(4-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **2.2a** (70 μL, 0.305 mmol, 3.0 equiv.) were premixed and stirred in DMF (1 mL) for 20 minutes at room temperature before being heated at 120 °C in an O_2 atmosphere (balloon) for 72.5 h. 2:1 Et_2O:EtOAc (30 mL) was added to the reaction and the reaction mixture was washed with H_2O (3×10 mL) and brine (10 mL). The combined organic layers were dried over $MgSO_4$ and solvent was removed by reduced pressure. The resulting crude was purified by silica gel column chromatography (20:1 → 5:1 hexane:EtOAc) to yield **2.4aa** (23.7 mg, 0.077 mmol, 77%) as a yellow powder.

Mp: 90-92 °C (hexane/EtOAc) (literature mp: 89-91 °C);[12] R_f: 0.36 in 3:1 petroleum ether/EtOAc; ν_{max}/cm^{-1}: 3080, 3012, 2920, 1733, 1715, 1684, 1604, 1564, 1508, 1422, 755, 702; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.75 (d, *J* = 8.9 Hz, 2H, Ar-H), 7.13 – 7.04 (m, 3H, Ar-H), 7.00 – 6.97 (m, 3H, Ar-H), 6.96 (s, 1H, =CH), 6.91 (d, *J* = 8.9 Hz, 2H, Ar-H), 3.84 (s, 3H, OCH_3), 3.06 (d, *J* = 13.4 Hz , 1H, C<u>H</u>HPh), 3.03 (d, *J* = 13.4 Hz, 1H, CH<u>H</u>Ph), 1.32 (s, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.1(C), 205.5 (C), 162.4 (C), 156.2 (C), 138.8 (CH), 136.1 (C), 131.1 (2 × CH), 129.8 (2 × CH), 128.4 (2 × CH), 127.0 (CH), 121.6 (C), 114.5 (2 × CH), 55.5 (CH_3), 54.0 (C), 41.6 (CH_2), 19.8 (CH_3).

2-Benzyl-2-methyl-4-phenylcyclopent-4-ene-1,3-dione 2.4ab[12]

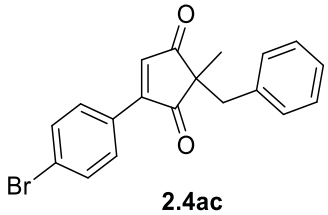


2.4ab

Conditions A: 2-Benzyl-2-methylcyclopentane-1,3-dione **2.1a** (20.3 mg, 0.100 mmol, 1.0 equiv.), 1,10-phenanthroline **2.38** (3.6 mg, 19.98 μmol, 0.2 equiv.), $Pd(OAc)_2$ (2.2 mg, 9.8 μmol, 0.1 equiv.) and 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane **2.2b** (60.4 mg, 0.296 mmol, 3.0 equiv.) were premixed and stirred in DMF (1 mL) for 20 minutes at room temperature before being heated to 120 °C under an O_2 atmosphere (balloon) for 71 h. 2:1 Et_2O:EtOAc (30 mL) was added to the reaction and the reaction mixture was washed with H_2O (2×10 mL) and brine (10 mL). The combined organic layers were dried over $MgSO_4$ and solvent was removed by reduced pressure. The resulting crude was purified by silica gel column chromatography (25:1 → 20:1 petroleum ether:EtOAc) to yield **2.4ab** (19.8 mg, 0.072 mmol, 72%) as a yellow crystalline solid.

Mp: 90-91 °C (petroleum ether/EtOAc) (literature mp: 91-93 °C);[12] R_f: 0.6 in 5:1 petrol ether: EtOAc; ν_{max}/ cm^{-1}:3083, 2920, 1732, 1684, 1586, 1598, 1568, 760, 700 str; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.70 – 7.65 (m, 2H, Ar-H), 7.46 – 7.36 (m, 3H, Ar-H), 7.16 – 7.07 (m, 3H, Ar-H), 7.04 (s, 1H, =CH), 7.00 – 6.95 (m, 2H, Ar-H), 3.07 (d, *J* = 13.1 Hz, 1H, C<u>H</u>HPh), 3.06 (d, *J* = 13.1 Hz, 1H, CH<u>H</u>Ph), 1.34 (s, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.5 (C), 205.7 (C), 157.2 (C), 141.2 (CH), 135.9 (C), 131.5 (CH), 129.8 (2 × CH), 129.13 (2 × CH), 129.12 (2 × CH), 128.9 (2 × CH), 128.4 (CH), 127.1 (CH), 54.1 (C), 41.7 (CH_2), 19.7 (CH_3).

2-Benzyl-4-(4-bromophenyl)-2-methylcyclopent-4-ene-1,3-dione 2.4ac

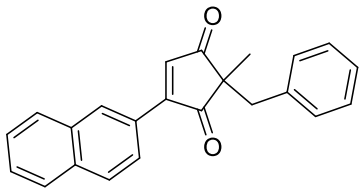


2.4ac

Conditions B: 2-Benzyl-2-methylcyclopentane-1,3-dione **2.1a** (20.3 mg, 0.100 mmol, 1.0 equiv.), 1,10-phenanthroline **2.38** (5.5 mg, 30.5 μmol, 0.31 equiv.), $Pd(OAc)_2$ (3.5 mg, 15.59 μmol, 0.16 equiv.) and 2-(4-bromophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **2.2c** (84.9 mg, 0.300 mmol, 3.0 equiv.) were premixed and stirred in DMF (1 mL) for 20 minutes at room temperature before being heated at 120 °C in an O_2 atmosphere (balloon) for 72.5 h. 2:1 Et_2O:EtOAc (30 mL) was added to the reaction and the reaction mixture was washed with H_2O (2×10 mL) and brine (10 mL). The combined organic layers were dried over $MgSO_4$ and solvent was removed by reduced pressure. The resulting crude was purified by silica gel column chromatography (40:1 → 30:1 petroleum ether:EtOAc) to yield **2.4ac** (24.2 mg, 0.068 mmol, 68%) as a yellow oil.

R_f: 0.7 in 5:1 petroleum ether:EtOAc; ν_{max}/cm^{-1}: 3030, 2926, 2360, 1742, 1694, 1589, 1557, 1485, 755, 830, 701; ^1H NMR (300 MHz, $CDCl_3$) δ 7.59 – 7.50 (m, 4H, Ar-H), 7.17 – 7.06 (m, 3H, Ar-H), 7.02 (s, 1H, =CH), 6.99 – 6.92 (m, 2H, Ar-H), 3.08 (d, *J* = 13.2 Hz, 1H, C<u>H</u>HPh), 3.03 (d, *J* = 13.2 Hz, 1H, CH<u>H</u>Ph) 1.33 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.3 (C), 205.5 (C), 155.9 (C), 141.2 (CH), 135.8 (C), 132.3 (2 × CH), 130.5 (2 × CH), 129.7 (2 × CH), 128.5 (2 × CH), 127.8 (C), 127.2 (CH), 126.4 (C), 54.1 (C), 41.8 (CH_2), 19.6 (CH_3); HRMS (TOF MS ASAP+) *m/z calc.* for $C_{19}H_{15}BrO_2$: 355.0334 $[M+H]^+$ found: 355.0333.

2-Benzyl-2-methyl-4-(naphthalen-2-yl)cyclopent-4-ene-1,3-dione 2.4ad[12]



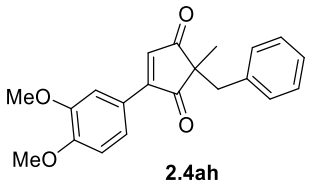
2.4ad

2-Benzyl-2-methylcyclopentane-1,3-dione **2.1a** (20.3 mg, 0.100 mmol, 1.0 equiv.), 1,10-phenanthroline **2.38** (3.6 mg, 20.0 μmol, 0.2 equiv.), $Pd(OAc)_2$ (2.3 mg, 10.2 μmol, 0.1 equiv.) and 4,4,5,5-tetramethyl-2-(naphthalen-2-yl)-1,3,2-dioxaborolane **2.2d** (76.4 mg, 0.300 mmol, 3.0 equiv.) were premixed and stirred in DMF (1 mL) for 20 minutes at room temperature before being heated at 120 °C in an O_2 atmosphere (balloon) for 69 h. 2:1 Et_2O:EtOAc (30 mL) was added to the reaction and the reaction mixture was washed with H_2O (3×10 mL) and brine (10 mL). The combined organic layers were dried over $MgSO_4$ and solvent was removed by reduced pressure. To aid in purification, the crude was then mixed in EtOAc (5 mL) and sat. K_2CO_3 (5 mL) for 0.5 h to remove phenolic side products, the organic layer was separated and washed with H_2O (2 x 10 mL). The combined organic layers were dried over $MgSO_4$ and solvent was removed by reduced pressure. The resulting crude was purified by silica gel column chromatography (25:1 → 20:1 petroleum ether:EtOAc) to yield **2.4ad** (26.7 mg, 0.086 mmol, 86%) as a yellow powder.

Mp: 124-126 °C (petroleum ether:EtOAc) (literature mp: 126-128 °C);[12] R_f: 0.5 in 5:1 petroleum ether:EtOAc; ν_{max}/cm^{-1}: 3058, 2918, 1736, 1690, 1600, 1581, 1565, 1495, 776, 749, 699; ^1H NMR (300 MHz, $CDCl_3$) δ 8.53 – 8.45 (m, 1H, Ar-H), 7.99 – 7.90 (m, 1H, Ar-H), 7.82 (m, 2H, Ar-H), 7.61 – 7.50 (m, 3H, Ar-H), 7.16 (s, 1H, =CH), 7.14 – 6.98 (m, 5H, Ar-H), 3.13 (d, *J* = 13.2 Hz, 1H, C<u>H</u>HPh), 3.07 (d, *J* = 13.3 Hz, 1H, CH<u>H</u>Ph), 1.38 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.8 (C), 205.7 (C), 156.7 (C), 141.1 (CH), 135.9 (C), 134.5 (C), 133.0 (C), 130.6 (CH), 129.8 (2 × CH), 129.5

(CH), 128.7 (CH), 128.5 (2 × CH), 128.2 (CH), 127.8 (CH), 127.1 (CH), 127.0 (CH), 126.3 (C), 125.0 (CH), 54.2 (C), 41.7 (CH_2), 19.8 (CH_3); HRMS (TOF MS ASAP+) *m/z calc.* for $C_{23}H_{19}O_2$: 327.1385 $[M+H]^+$; found: 327.1381.

2-Benzyl-4-(3,4-dimethoxyphenyl)-2-methylcyclopent-4-ene-1,3-dione 2.4ah[12]

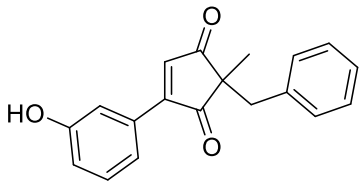


2.4ah

Conditions B: 2-Benzyl-2-methylcyclopentane-1,3-dione **2.1a** (20.3 mg, 0.100 mmol, 1.0 equiv.), 1,10-phenanthroline **2.38** (5.4 mg, 30.0 μmol, 0.3 equiv.), $Pd(OAc)_2$ (3.4 mg, 15.5 μmol, 0.16 equiv.) and 2-(3,4-dimethoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **2.2h** (80.2 mg, 0.304 mmol, 3.0 equiv.) were premixed and stirred in DMF (1 mL) for 20 minutes at room temperature before being heated at 120 °C in an O_2 atmosphere (balloon) for 71 h. 2:1 Et_2O:EtOAc (30 mL) was added to the reaction and the reaction mixture was washed with H_2O (3×10 mL) and brine (10 mL). The combined organic layers were dried over $MgSO_4$ and solvent was removed by reduced pressure. The resulting crude was purified by silica gel column chromatography (4:1→2:1 hexane:EtOAc) to yield **2.4ah** (19.1 mg, 56.8 mmol, 57%) as a yellow oil.

R_f: 0.3 in 3:1 petrol ether:EtOAc; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (dd, *J* = 8.5, 2.0 Hz, 1H, Ar-H), 7.31 (d, *J* = 2.0 Hz, 1H, Ar-H), 7.15 – 7.06 (m, 3H, Ar-H), 7.01 – 6.94 (m, 3H, ArH and =CH), 6.88 (d, *J* = 8.5 Hz, 1H, Ar-H), 3.92 (s, 3H, OMe), 3.90 (s, 3H, OMe), 3.05 (apparent s, 2H, CH_2Ph), 1.33 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.1 (C), 205.4 (C), 156.2 (C), 152.2 (C), 149.3 (C), 139.0 (CH), 136.1 (C), 129.9 (2 × CH), 128.4 (2 × CH), 127.1 (CH), 123.4 (CH), 121.9 (C), 111.9 (CH), 111.3 (CH), 56.2 (2 × CH_3), 54.2 (C), 41.7 (CH_2), 19.9 (CH_3); HRMS (FTMS + p NSI) *m/z calc.* for $C_{21}H_{21}O_4$: 377.1434 $[M+H]^+$; found: 377.1438

2-Benzyl-4-(3-hydroxyphenyl)-2-methylcyclopent-4-ene-1,3-dione 2.4ai



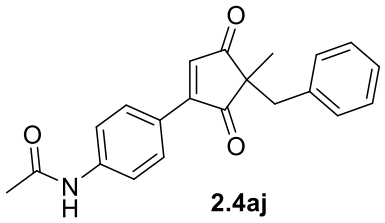
2.4ai

Conditions B: 2-Benzyl-2-methylcyclopentane-1,3-dione **2.1a** (20.4 mg, 0.101 mmol, 1.0 equiv.), 1,10-phenanthroline **2.38** (5.4 mg, 30.0 μmol, 0.3 equiv.), $Pd(OAc)_2$ (3.4 mg, 15.1 μmol, 0.15 equiv.) and 2-(3,4-dimethoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **2.2i** (66.1 mg, 0.300 mmol, 2.98 equiv.) were premixed and stirred in DMF (1 mL) for 20 minutes at room temperature before being heated at 120 °C in an O_2 atmosphere (balloon) for 71 h. 2:1 Et_2O:EtOAc (30 mL) was added to the reaction and the reaction mixture was washed with H_2O (3×10 mL) and brine (10 mL). The combined organic layers were dried over $MgSO_4$ and solvent was removed by reduced pressure. The resulting crude was purified by silica gel column chromatography (10:1→5:1 hexane:EtOAc + 1% toluene) to yield **2.2ai** (22.3 mg, 76.3 mmol, 78% yield at ~80% purity, NMR yield 63% with internal standard 1,3,5-trimethoxybenzene) as a yellow oil. Material was purified for characterisation (8.5 mg), the additional material (13.8 mg) was subjected to an acid and base wash to purify the additional material to limited success.

R_f: 0.24 in 3:1 petrol ether:EtOAc; ν_{max}/cm^{-1}: 3280 br, 3076, 2919, 1729, 1675, 1588, 1571, 1489, 884, 795 str, 700; ^1H NMR (300 MHz, $CDCl_3$) δ 7.30 – 7.26 (m, 2H, Ar-H and $CDCl_3$), 7.22 (dt, *J* = 7.8, 1.3 Hz, 1H, Ar-H), 7.15 – 7.07 (m, 3H, Ar-H), 7.03 (s, 1H, =CH), 6.98 – 6.91 (m, 3H, Ar-H), 5.24 (s, 1H, PhOH), 3.10 (d, *J* = 13.4 Hz, 1H, C<u>H</u>HPh), 3.06 (d, *J* = 13.1 Hz, 1H, CH<u>H</u>Ph), 1.34 (broad s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.5 (C), 205.7 (C), 156.7 (C), 155.9 (C), 141.5 (CH), 135.9 (C), 130.4 (C), 130.3 (CH), 129.8 (2 × CH), 128.5 (2 × CH), 127.2 (CH), 121.7 (CH), 118.7 (CH),

115.9 (CH), 54.2 (C), 41.7 (CH_2), 19.7 (CH_3); HRMS (FTMS + p NSI) *m/z calc.* for $C_{19}H_{17}O_3$: 293.1172 $[M+H]^+$; found: 293.1176.

_N_-(4-(4-Benzyl-4-methyl-3,5-dioxocyclopent-1-en-1-yl)phenyl)acetamide 2.4aj[12]



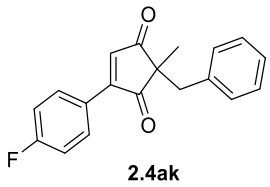
2.4aj

Conditions A: 2-Benzyl-2-methylcyclopentane-1,3-dione **2.1a** (20.3 mg, 0.100 mmol, 1.0 equiv.), 1,10-phenanthroline **2.38** (3.6 mg, 19.98 μmol, 0.2 equiv.), $Pd(OAc)_2$ (2.2 mg, 9.8 μmol, 0.10 equiv.) and N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide **2.2j** (78.0 mg, 0.299 mmol, 2.9 equiv.) were premixed and stirred in DMF (1 mL) for 20 minutes at room temperature before being heated at 120 °C in an O_2 atmosphere (balloon) for 72.5 h. 2:1 Et_2O:EtOAc (30 mL) was added to the reaction and the reaction mixture was washed with H_2O (2×10 mL) and brine (10 mL). The combined organic layers were dried over $MgSO_4$ and solvent was removed by reduced pressure. The resulting crude was purified by silica gel column chromatography (5:1 → 2:1 hexanes:EtOAc) to yield **2.4aj** (15.6 mg, 0.047 mmol, 47%) as a yellow oil.

R_f: 0.27 in 1:1 petroleum ether:EtOAc; ν_{max}/cm^{-1}: 3306 br, 3031, 2925, 1739, 1689, 1592 str, 1508 str, 1410, 755, 700; ^1H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.3 Hz, 2H, Ar-H), 7.56 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.43 (s, 1H, NH), 7.13 – 7.05 (m, 3H, Ar-H), 6.99 (s, 1H, =CH), 6.98 – 6.92 (m, 2H, Ar-H), 3.08 (d, *J* = 13.7 Hz, 1H, C<u>H</u>HPh), 3.01 (d, *J*, = 13.7 Hz, 1H, CH<u>H</u>Ph), 2.19 (s, 3H, CH_3C=O), 1.32 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.8 (C), 205.6 (C), 168.6 (C), 156.0 (C), 140.9 (C), 139.9 (CH), 135.9 (C), 130.3 (2 × CH), 129.8 (2 × CH), 128.4 (2 × CH), 127.1 (CH), 124.6 (C),

119.5 (CH), 54.1 (C), 41.7 (CH_2), 24.9 (CH_3), 19.7 (CH_3); HRMS (NSI) *m/z* calc. for $C_{21}H_{19}NO_3$: 334.1442 $[M+H]^+$ found: 334.1438.

2-Benzyl-4-(4-fluorophenyl)-2-methylcyclopent-4-ene-1,3-dione 2.4ak

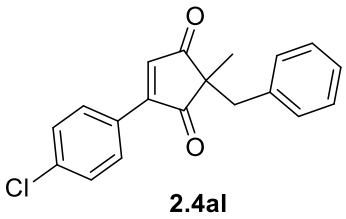


2.4ak

Conditions B: 2-Benzyl-2-methylcyclopentane-1,3-dione **2.1a** (20.3 mg, 0.100 mmol, 1.0 equiv.), 1,10-phenanthroline **2.38** (5.5 mg, 30.5 μmol, 0.3 equiv.), $Pd(OAc)_2$ (3.5 mg, 15.6 μmol, 0.16 equiv.) and 2-(4-fluorophenyl)-4,4,5,5-tetramethyl- 1,3,2-dioxaborolane **2.2k** (67.8 mg, 0.305 mmol, 3.0 equiv.) were premixed and stirred in DMF (1 mL) for 20 minutes at room temperature before being heated at 120 °C in an O_2 atmosphere (balloon) for 69 h. 2:1 Et_2O:EtOAc (30 mL) was added to the reaction and the reaction mixture was washed with H_2O (3×10 mL) and brine (10 mL). The combined organic layers were dried over $MgSO_4$ and solvent was removed by reduced pressure. The resulting crude was purified by silica gel column chromatography (20:1 hexane:EtOAc) to yield **2.4ak** (20.6 mg, 70.0 mmol, 70%) as a yellow oil.

R_f: 0.7 in 3:1 petrol ether:EtOAc; ν_{max}/cm^{-1}: 2928, 1742, 1694, 1601, 1505 str, 1452, 841 str, 753, 701; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 – 7.68 (m, 2H, Ar-H), 7.15 – 7.04 (m, 5H, Ar-H), 7.00 (s, 1H, =CH), 6.99 – 6.93 (m, 2H, Ar-H), 3.06 (apparent s, 2H, CH_2Ph), 1.33 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.5 (C), 205.4 (C), 164.7 (d, ^1J = 253.6 Hz, C), 155.8 (C), 140.7 (CH), 135.9 (C), 131.40 (d, ^3J = 8.9 Hz, 2 × CH), 129.8 (2 × CH), 128.5 (2 × CH), 127.2 (CH), 125.3 (d, ^4J = 3.4 Hz, C), 116.2 (d, ^2J = 21.6 Hz, 2 × CH), 54.1 (C), 41.8 (CH_2), 19.7 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ -107.03 – -107.21 (m, Ar-F); HRMS (TOF MS ASAP+) *m/z calc.* for $C_{19}H_{15}FO_2$: 295.1134 $[M+H]^+$; found: 295.1129.

2-Benzyl-4-(4-chlorophenyl)-2-methylcyclopent-4-ene-1,3-dione 2.4al

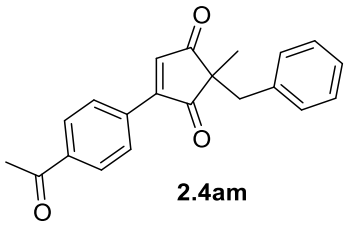


2.4al

Conditions B: 2-Benzyl-2-methylcyclopentane-1,3-dione **2.1a** (20.3 mg, 0.100 mmol, 1.0 equiv.), 1,10-phenanthroline **2.38** (5.5 mg, 30.5 μmol, 0.31 equiv.), $Pd(OAc)_2$ (3.5 mg, 15.59 μmol, 0.16 equiv.) and 2-(4-chlorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **2.2l** (71.5 mg, 0.300 mmol, 3.0 equiv.) were premixed and stirred in DMF (1 mL) for 20 minutes at room temperature before being heated at 120 °C in an O_2 atmosphere (balloon) for 69 h. 2:1 Et_2O:EtOAc (30 mL) was added to the reaction and the reaction mixture was washed with H_2O (3×10 mL) and brine (10 mL). The combined organic layers were dried over $MgSO_4$ and solvent was removed by reduced pressure. The resulting crude was purified by silica gel column chromatography (30:1 → 20:1 petroleum ether:EtOAc) to yield **2.4al** (26.7 mg, 0.086 mmol, 86%) as a yellow oil.

R_f: 0.48 in 5:1 petroleum ether/EtOAc; ν_{max}/cm^{-1}:2925, 1741, 1694, 1595, 1559, 1489, 834, 756, 701; ^1H NMR (300 MHz, $CDCl_3$) δ 7.67 – 7.60 (d, J = 8.6 Hz, 2H, Ar-H), 7.41 – 7.34 (d, J = 8.6 Hz, 2H, Ar-H), 7.13 – 7.06 (m, 3H, Ar-H), 7.02 (s, 1H, =CH), 6.98 – 6.92 (m, 3H, Ar-H), 3.06 (apparent s, 2H, CH_2Ph), 1.33 (s, 2H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.3 (C), 205.5 (C), 155.8 (C), 141.3 (CH), 137.9 (C), 135.8 (C), 130.4 (2 × CH), 129.7 (2 × CH), 129.3 (2 × CH), 128.5 (2 × CH), 127.4 (C), 127.2 (CH), 54.1 (C), 41.8 (CH_2), 19.6 (CH_3); HRMS (TOF MS ASAP+) *m/z* calc. for $C_{19}H_{15}ClO_2$: 3110839 $[M+H]^+$ found: 311.0842.

4-(4-Acetylphenyl)-2-benzyl-2-methylcyclopent-4-ene-1,3-dione 2.4am[12]



2.4am

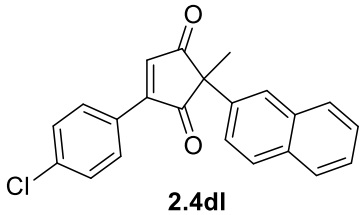
Conditions B: 2-Benzyl-2-methylcyclopentane-1,3-dione **2.1a** (20.3 mg, 0.100 mmol, 1.0 equiv.), 1,10-phenanthroline **2.38** (5.4 mg, 29.97 μmol, 0.30 equiv.), $Pd(OAc)_2$ (3.4 mg, 15.15 μmol, 0.15 equiv.) and 1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethan-1-one **2.2m** (74.2 mg, 0.300 mmol, 3.0 equiv.) were premixed and stirred in DMF (1 mL) for 20 minutes at room temperature before being heated at 120 °C in an O_2 atmosphere (balloon) for 72.5 h. 2:1 Et_2O:EtOAc (30 mL) was added to the reaction and the reaction mixture was washed with H_2O (3×10 mL) and brine (10 mL). The combined organic layers were dried over $MgSO_4$ and solvent was removed by reduced pressure. The resulting crude was stirred in EtOAc (5mL) and HCl (0.1 M, 5 mL) overnight. The aqueous layer was washed with EtOAc (10 mL) and the combined organic layers were then stirred in sat. K_2CO_3 (15 mL) for 30 minutes at 30 °C. The above acid followed by base wash was carried out to remove any co-eluting pinacol boronic ester and corresponding phenol. The aqueous layer was washed with EtOAc and the organic layer was dried over $MgSO_4$ and solvent was removed by reduced pressure. The resulting crude was purified by silica gel column chromatography (5:1 → 3:1 hexanes:EtOAc) to yield **2.4am** (10.7 mg, 0.018 mmol, 18%) as a yellow oil.

R_f: 0.36 in 5:1 petroleum ether/EtOAc; ^1H NMR (300 MHz, $CDCl_3$) δ 7.93 – 7.86 (d, J = 8.2 Hz, 2H, Ar-H), 7.70 – 7.64 (d, J = 8.2 Hz 2H, Ar-H), 7.06 – 7.00 (m, 3H, Ar-H), 6.95 – 6.84 (m, 2H, Ar-H), 3.00 (apparent s, 2H, CH_2Ph), 2.54 (s, 3H, $C(O)CH_3$), 1.28 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.0 (C), 205.5 (C), 197.4 (C), 156.1 (C), 142.5 (CH), 138.9 (C), 135.8 (C), 133.2 (C), 129.8 (2 × CH), 129.3 (2 × CH), 128.6 (2

× CH), 128.5 (2 × CH), 127.3 (CH), 54.2 (C), 42.0 (CH_2), 26.8 (CH_3), 19.5 (CH_3); HRMS (FTMS p NSI) *m/z* calc. for $C_{21}H_{19}O_3$: 319.1329 $[M+H]^+$ found: 319.1333.

2.9.4 2,2-Disubstituted Cyclopentanedione Scope

4-(4-Chlorophenyl)-2-methyl-2-(naphthalene-2-yl)cyclopent-4-ene-1,3-dione 2.4dl[12]



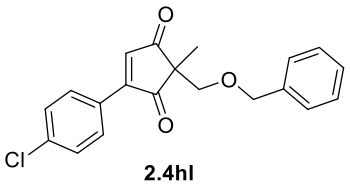
2.4dl

2-Methyl-2-(naphthalene-2-yl)cyclopentane-1,3-dione **2.1d** (23.8 mg, 0.099 mmol, 1.0 equiv.), 1,10-phenanthroline **2.38** (5.4 mg, 30.0 μmol, 0.3 equiv.), $Pd(OAc)_2$ (3.4 mg, 15.1 μmol, 0.15 equiv.) and 2-(4-chlorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **2.2l** (72.0mg, 0.302 mmol, 3.0 equiv.) were premixed and stirred in DMF (1 mL) for 20 minutes at room temperature before being heated at 120 °C in an O_2 atmosphere (balloon) for 71 h. 2:1 Et_2O:EtOAc (30 mL) was added to the reaction and the reaction mixture was washed with H_2O (3×10 mL) and brine (10 mL). The combined organic layers were dried over $MgSO_4$ and solvent was removed by reduced pressure. The resulting crude was purified by silica gel column chromatography (30:1 hexane:EtOAc) to yield **2.4dl** (24.4 mg, 0.0703 mmol, 71%) as a yellow solid.

Mp: 134-136 °C (hexane/EtOAc) (literature mp: 130-135 °C);[12] R_f: 0.41 in 5:1 petroleum ether:EtOAc; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.7 Hz, 2H, Ar-H), 7.86 – 7.76 (m, 4H, Ar-H), 7.52 – 7.45 (m, 6H, Ar-H), 1.75 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.9 (C), 203.3 (C), 155.0 (C), 140.5 (CH), 138.4 (C), 134.7 (C), 133.3 (C), 132.7 (C), 130.8 (2 × CH), 129.5 (2 × CH), 128.9 (CH), 128.3 (CH), 127.7 (CH), 127.5 (C), 126.6 (2 × CH), 125.8 (CH), 124.1 (CH), 56.4 (C), 20.2 (CH_2), 1.2 (CH_3);

HRMS (TOP MS ASAP+) *m/z calc.* for $C_{22}H_{16}ClO_2$: 347.0833 $[M+H]^+$; found: 347.0835.

2-((Benzyloxy)methyl)-4-(4-chlorophenyl)-2-methylcyclopent-4-ene-1,3-dione 2.4hl



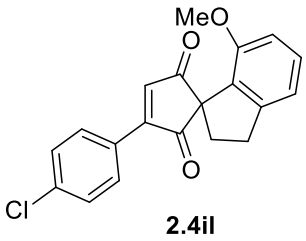
2.4hl

2-((Benzyloxy)methyl)-2-methylcyclopentane-1,3-dione **2.1h** (23.4 mg, 0.101 mmol, 1.0 equiv.), 1,10-phenanthroline **2.38** (5.3 mg, 29.4 μmol, 0.3 equiv.), $Pd(OAc)_2$ (3.4 mg, 15.1 μmol, 0.15 equiv.) and 2-(4-chlorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **2.2l** (71.4 mg, 0.299 mmol, 3.0 equiv.) were premixed and stirred in DMF (1 mL) for 20 minutes at room temperature before being heated at 120 °C in an O_2 atmosphere (balloon) for 71 h. 2:1 Et_2O:EtOAc (30 mL) was added to the reaction and the reaction mixture was washed with H_2O (3×10 mL) and brine (10 mL). The combined organic layers were dried over $MgSO_4$ and solvent was removed by reduced pressure. The resulting crude was purified by silica gel column chromatography (15:1 hexane:EtOAc). The solvent was removed by reduced pressure and co-eluted *p*-chlorophenol was removed by stirring product fractions over carbonate on polymer support beads (177 mg, 0.62 mmol) in DCM (0.5 mL) overnight and filtered to **2.4hl** (18.5 mg, 0.054 mmol, 54%) as a yellow oil.

R_f: 0.4 in 5:1 petroleum ether:EtOAc; ν_{max}/cm^{-1}: 2858, 1746, 1698 s, 1595, 1559, 1486, 1453, 1290, 1092 s, 836, 778, 697; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.92 (d, *J* = 8.7 Hz, 2H, Ar-H), 7.47 (d, *J* = 8.7 Hz, 2H, Ar-H), 7.40 (s, 1H, =CH), 7.30 – 7.23 (m, 3H, Ar-H), 7.14 – 7.10 (m, 2H, Ar-H), 4.39 (s, 2H, CH_2Ph), 3.69 (d, J = 8.5 Hz, 1H, C<u>H</u>HOBn), 3.69 (d, J = 8.5 Hz, 1H, CH<u>H</u>OBn), 1.11 (s, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 205.3 (C), 204.4 (C), 156.0 (C), 141.6 (CH), 138.0 (C), 137.6 (C), 130.7 (2 × CH),

129.4 (2 × CH), 128.5 (2 × CH), 127.9 (CH), 127.8 (2 × CH), 127.4 (CH), 73.6 (CH_2), 72.5 (CH_2), 53.0 (C), 15.4 (CH_3); HRMS (TOP MS ASAP+) *m/z calc.* for $C_{20}H_{18}ClO_3$: 341.0944 $[M+H]^+$; found: 341.0941.

3-(4-Chlorophenyl)-7'-methoxy-2',3'-dihydrospiro[cyclopentane-1,1'-inden]-3-ene-2,5-dione 2.4il



2.4il

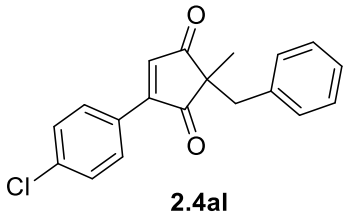
7'-Methoxy-2',3'-dihydrospiro[cyclopentane-1,1'-indene]-2,5-dione **2.4il** (23.0 mg, 0.099 mmol, 1.0 equiv.), 1,10-phenanthroline **2.38** (5.3 mg, 30.1 μmol, 0.3 equiv.), $Pd(OAc)_2$ (3.4 mg, 15.1 μmol, 0.15 equiv.) and 2-(4-chlorophenyl)-4,4,5,5- tetramethyl-1,3,2-dioxaborolane **2.2l** (71.9 mg, 0.301 mmol, 3.0 equiv.) were premixed and stirred in DMF (1 mL) for 20 minutes at room temperature before being heated at 120 °C in an O_2 atmosphere (balloon) for 71 h. 2:1 Et_2O:EtOAc (30 mL) was added to the reaction and the reaction mixture was washed with H_2O (3×10 mL) and brine (10 mL). The combined organic layers were dried over $MgSO_4$ and solvent was removed by reduced pressure. The resulting crude was purified by silica gel column chromatography (8:1 hexane:EtOAc). Solvent was removed by reduced pressure and co-eluted *p*-chlorophenol was removed by stirring product fractions over carbonate on polymer support beads (47.2 mg, 0.165 mmol) in DCM (0.5 mL) for 1 h and filtered to yield **2.4il** (22.9 mg, 0.068 mmol, 68%) as a yellow amorphous solid.

R_f: 0.4 in 5:1 petroleum ether:EtOAc; ν_{max}/cm^{-1}: 2933, 2850, 1741, 1695 s, 1560, 1479, 1091, 822, 733, 703; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.93 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.48 (d, *J* = 8.7 Hz, 2H, Ar-H), 7.37 (s, 1H, =CH), 7.22 (t, *J* = 7.8 Hz, 1H, Ar-H), 6.92 (dd, *J* = 7.5, 0.9 Hz, 1H, Ar-H), 6.60 (d, *J* = 8.0 Hz, 1H, Ar-H), 3.57 (s, 3H, OCH_3),

3.34 – 3.11 (m, 2H, CH_2), 2.50 – 2.32 (m, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 205.0 (C), 204.4 (C), 155.3 (C), 155.1 (C), 148.3 (C), 140.1 (CH), 137.8 (C), 130.6 (2 × CH), 130.5 (CH), 129.4 (2 × CH), 128.2 (C), 128.1 (C), 117.6 (CH), 108.6 (CH), 62.9 (C), 55.5 (CH_3), 34.5 (CH_2), 32.42 (CH_2); HRMS (FTMS p NSI) *m/z calc.* for $C_{20}H_{16}ClO_3$: 339.0782 $[M+H]^+$; found: 339.0786.

2.9.5 Continuous Flow Reactions

2-Benzyl-4-(4-chlorophenyl)-2-methylcyclopent-4-ene-1,3-dione 2.4al



2.4al

0.1 mmol scale:

2-Benzyl-2-methylcyclopentane-1,3-dione **2.1a** (30.3, 0.15 mmol, 1.0 equiv.), 1,10-phenanthroline **2.38** (8.1 mg, 0.045 mmol, 0.3 equiv.), $Pd(OAc)_2$ (4.1 mg, 0.023 mmol, 0.15 equiv.) and *p*-chlorophenyl Bpin **2.2l** (107.3 mg, 0.45 mmol, 3.0 equiv.) were stirred in DMF (1.5 mL) for 20 minutes at room temperature. The homogeneous reaction mixture was pumped at a flow rate of 0.4 mL min^{-1} and molecular oxygen was pumped at a flow rate of 0.4 mL min^{-1} to a T-junction. The reaction/oxygen mixture was cycled through the 120 °C reactor 120 °C reactor (2 mL volume, residency time 2.5 min) for 72 h. 2:1 Et_2O:EtOAc (30 mL) was added to the reaction and the reaction mixture was washed with H_2O (2×10 mL) and brine (10 mL). The combined organic layers were dried over $MgSO_4$ and solvent was removed by reduced pressure to yield crude **2.4al (**55% ^1H NMR yield by comparison of 1,3,5-trimethoxybenzene as internal standard, 0.82 mmol).

For characterisation, please see the racemic ATC batch reaction.

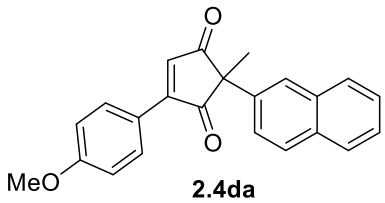
1.0 mmol scale:

2-Benzyl-2-methylcyclopentane-1,3-dione **2.1a** (202.3, 1.00 mmol, 1.0 equiv.), 1,10-phenanthroline **2.38** (54.1 mg, 0.300 mmol, 0.3 equiv.), $Pd(OAc)_2$ (33.8 mg, 0.15 mmol, 0.15 equiv.) and *p*-chlorophenyl Bpin **2.2l** (718.1 mg, 3.01 mmol, 3.0 equiv.) were stirred in DMF (7.5mL) for 20 minutes at room temperature. The homogeneous reaction mixture was pumped at a flow rate of 0.4 mL min^{-1} and molecular oxygen was pumped at a flow rate of 0.4 mL min^{-1} to a T-junction. The reaction/oxygen mixture and was cycled through the 120 °C reactor (10 mL volume, residency time 12.5 min) for 72 h. 2:1 Et_2O:EtOAc (30 mL) was added to the reaction and the reaction mixture was washed with H_2O (2×10 mL) and brine (10 mL). The combined organic layers were dried over $MgSO_4$ and solvent was removed by reduced pressure to yield crude **2.4al (**55% ^1H NMR yield by comparison of 1,3,5-trimethoxybenzene as internal standard, 0.82 mmol).

For characterisation, please see the racemic ATC batch reaction.

2.9.6 Enantioselective Reactions

4-(4-Methoxyphenyl)-2-methyl-2-(naphthalen-2-yl)cyclopent-4-ene-1,3-dione 2.4da



2.4da

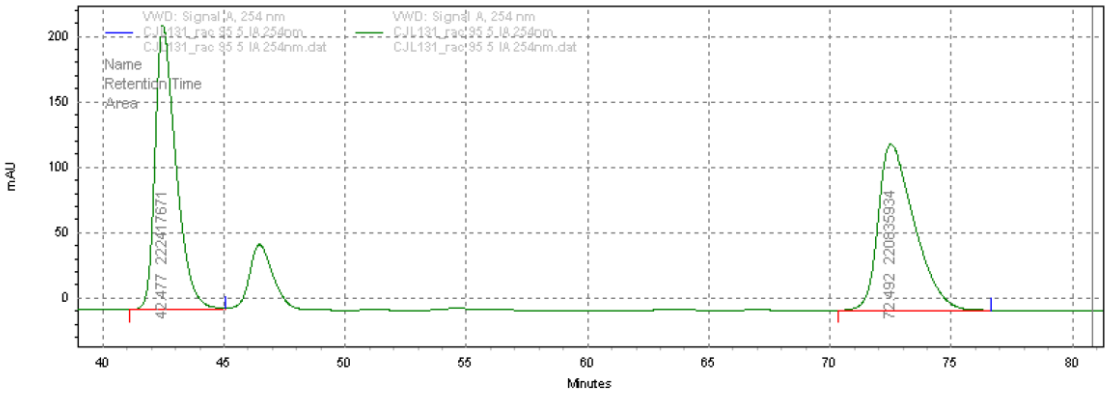
One-pot dehydrogenation/oxidative Heck desymmetrisation procedure

2-Methyl-2-(naphthalene-2-yl)cyclopentane-1,3-dione **2.1d** (23.8 mg, 0.099 mmol, 1.0 equiv.), 5-CF_3-^{t}BuPyOx **2.7** (5.4 mg, 20.0 μmol, 0.2 equiv.), $Pd(OAc)_2$ (2.2 mg, 9.8 μmol, 0.10 equiv.) were premixed and stirred in DMA (0.5 mL) for 20 minutes at room temperature before being heated at 120 °C in an O_2 atmosphere (balloon) for 72 h. $Pd(OAc)_2$ (2.2 mg, 9.8 μmol, 0.10 equiv.) and 5-CF_3-^{t}BuPyOx **2.7** (3.0mg, 11.4 μmol,

0.11 equiv.) were pre-mixed in DMA (0.1 mL) for 1 h. Para-methoxyphenyl boronic acid was dehydrated under vacuum with a heat gun to the corresponding boroxine **2.5a**, and this was added to the reaction (47.0 mg, 0.309 mmol, 3 equiv.) along with the catalyst mixture and DMA (0.4 mL). The reaction mixture was stirred at 50 °C under an atmosphere of O_2 (balloon) for 94 h. 2:1 Et_2O:EtOAc (30 mL) was added to the reaction and the reaction mixture was washed with H_2O (3×10 mL) and brine (10 mL). The combined organic layers were dried over $MgSO_4$ and solvent was removed by reduced pressure. The resulting crude was purified by silica gel column chromatography (10:1 hexane:EtOAc) and co-eluted *p*-MeO-phenol was removed by stirring product fractions over carbonate on polymer support beads (177 mg, 0.62 mmol) in DCM (0.5 mL) overnight and filtered to yield **2.4da** (20.4 mg, 0.06 mmol, 60%, 74:26 e.r.) as a yellow powder.

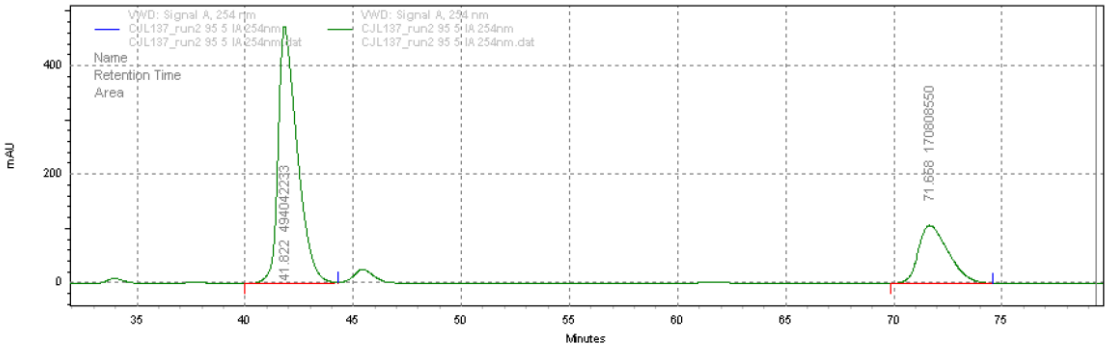
See racemic reaction for characterisation.

$[\alpha]_D^{21}$ = +47.1 (*c* 0.34, $CHCl_3$); 74:26 e.r.; HPLC (CHIRALPAK IA, hexane:2-propanol: 95:5, flow rate: 1.0 mL min^{-1}, detection UV 254 nm, 25 °C) t_R of major isomer: 41.8 min, t_R of minor isomer: 71.7 min.



VWD: Signal A, 254 nm Results

Retention Time	Area	Area %	Height	Height %
42.477	222417671	50.18	3639814	63.10
72.492	220835934	49.82	2128496	36.90
Totals	443253605	100.00	5768310	100.00



VWD: Signal A, 254 nm Results

Retention Time	Area	Area %	Height	Height %
41.822	494042233	74.31	7937449	81.63
71.658	170808550	25.69	1786744	18.37
Totals	664850783	100.00	9724193	100.00

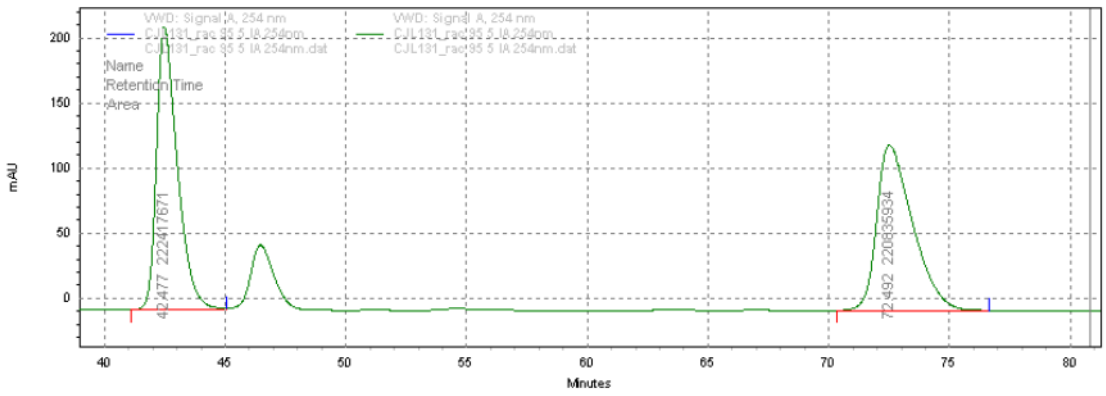
Telescoped dehydrogenation/oxidative Heck desymmetrisation procedure

2-Methyl-2-(naphthalene-2-yl)cyclopentane-1,3-dione **2.1d** (23.8 mg, 0.099 mmol, 1.0 equiv.), 5-CF_3-^{t}BuPyOx **2.7** (5.4 mg, 20.0 μmol, 0.2 equiv.), $Pd(OAc)_2$ (2.2 mg, 9.8 μmol, 0.10 equiv.) were premixed and stirred in DMA (0.5 mL) for 20 minutes at room temperature before being heated at 120 °C in an O_2 atmosphere (balloon) for 72 h. The reaction mixture was filtered through a short silica plug with 2:1 hexane:EtOAc and the

solvent was removed by reduced pressure. $Pd(OAc)_2$ (2.2 mg, 9.8 μmol, 0.10 equiv.) and 5-CF_3-^{t}BuPyOx **2.7** (3.0mg, 11.4 μmol, 0.11 equiv.) were pre-mixed in DMA (0.2 mL) for 1 h. *Para*-methoxyphenyl boronic acid was dehydrated under vacuum with a heat gun to the corresponding boroxine **2.5a**, and this was added to the reaction (47.0 mg, 0.309 mmol, 3 equiv.) along with the catalyst mixture and DMA (0.8 mL). The reaction mixture was stirred at 50 °C under an atmosphere of O_2 (balloon) for 94 h. 2:1 Et_2O:EtOAc (30 mL) was added to the reaction and the reaction mixture was washed with H_2O (3×10 mL) and brine (10 mL). The combined organic layers were dried over $MgSO_4$ and solvent was removed by reduced pressure. The resulting crude was purified by silica gel column chromatography (10:1 hexane:EtOAc) and co-eluted *p*-MeO-phenol was removed by stirring product fractions over carbonate on polymer support beads (177 mg, 0.62 mmol) in DCM (0.5 mL) overnight and filtered to yield **2.4da** (23.7 mg, 0.07 mmol, 70%, 88:12 e.r.) as a yellow powder.

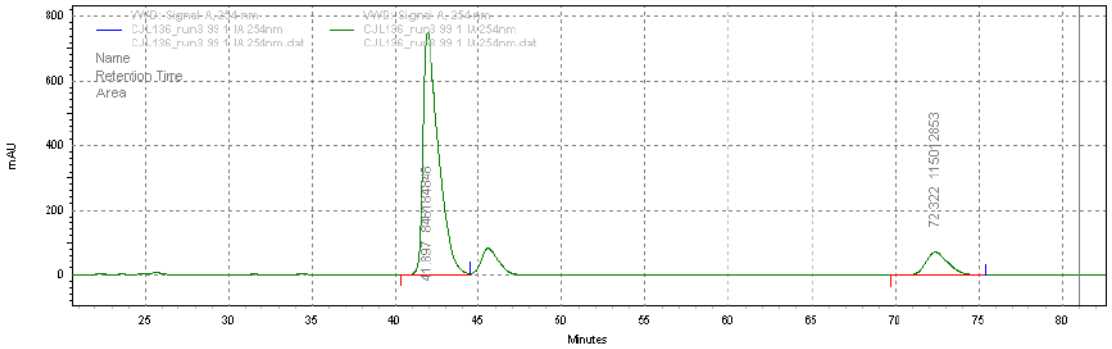
See racemic reaction for characterisation.

$[\alpha]_D^{21}$ = +100.0 (*c* 0.68, $CHCl_3$); 88:12 e.r.; HPLC (CHIRALPAK IA, hexane:2-propanol: 95:5, flow rate: 1.0 mL min^{-1}, detection UV 254 nm, 25 °C) t_R of major isomer: 41.9 min, t_R of minor isomer: 72.3 min.



VWD: Signal A, 254 nm Results

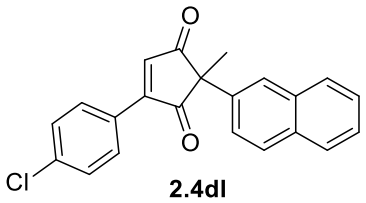
Retention Time	Area	Area %	Height	Height %
42.477	222417671	50.18	3639814	63.10
72.492	220835934	49.82	2128496	36.90
Totals	443253605	100.00	5768310	100.00



VWD: Signal A, 254 nm Results

Retention Time	Area	Area %	Height	Height %
41.897	846184848	88.03	12616201	91.14
72.322	115012853	11.97	1226107	8.86
Totals	961197701	100.00	13842308	100.00

4-(4-Chlorophenyl)-2-methyl-2-(naphthalen-2-yl)cyclopent-4-ene-1,3-dione 2.4dl[12]



2.4dl

One-pot dehydrogenation/oxidative Heck desymmetrisation procedure

2-Methyl-2-(naphthalene-2-yl)cyclopentane-1,3-dione **2.1d** (23.8 mg, 0.099 mmol, 1.0 equiv.), 5-CF_3^{t}BuPyOx **2.7** (5.4 mg, 20.0 μmol, 0.2 equiv.), $Pd(OAc)_2$ (2.2 mg, 9.8 μmol, 0.10 equiv.) were premixed and stirred in DMA (1 mL) for 20 minutes at room temperature before being heated at 120 °C in an O_2 atmosphere (balloon) for 72 h. $Pd(OAc)_2$ (2.2 mg, 9.8 μmol, 0.10 equiv.) and 5-CF_3^{t}BuPyOx **2.7** (3.0mg, 11.4 μmol, 0.11 equiv.) were pre-mixed in DMA (0.1 mL) for 1 h. *Para*-chlorophenyl boronic acid was dehydrated under vacuum with a heat gun to the corresponding boroxine **2.5l**, and this was added to the reaction (47.5 mg, 0.309 mmol, 3.0 equiv.) along with the catalyst mixture. The reaction mixture was stirred at 50 °C under an atmosphere of O_2 (balloon) for 92 h. 2:1 Et_2O:EtOAc (30 mL) was added to the reaction and the reaction mixture was washed with H_2O (3×10 mL) and brine (10 mL). The combined organic layers were dried over $MgSO_4$ and solvent was removed by reduced pressure. The resulting crude was purified by silica gel column chromatography (20:1 →10:1 hexane:EtOAc) to yield **2.4da** (20.4 mg, 0.06 mmol, 60%, 64:36) as a yellow powder.

See racemic reaction for characterisation.

$[\alpha]_D^{20.5}$ = +18.5 (*c* 0.54, $CHCl_3$); 64:36 e.r.; HPLC (CHIRALPAK IB, hexane:2-propanol: 99:1, flow rate: 1.0 mL min^{-1}, detection UV 254 nm, 25 °C) t_R of major isomer: 27.7 min, t_R of minor isomer: 21.5 min.

2.10 References

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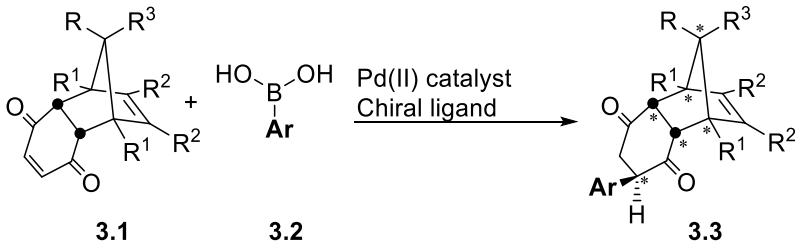
Chapter 3: Development of a Palladium(II)-Catalysed Desymmetrisation Reaction to Form Multiple Stereocentres



- Desymmetrisation of up to 5 stereogenic centres
- Creation of another stereocentre with a conjugate addition reaction
- Excellent e.r.s and good yields

Acknowledgements

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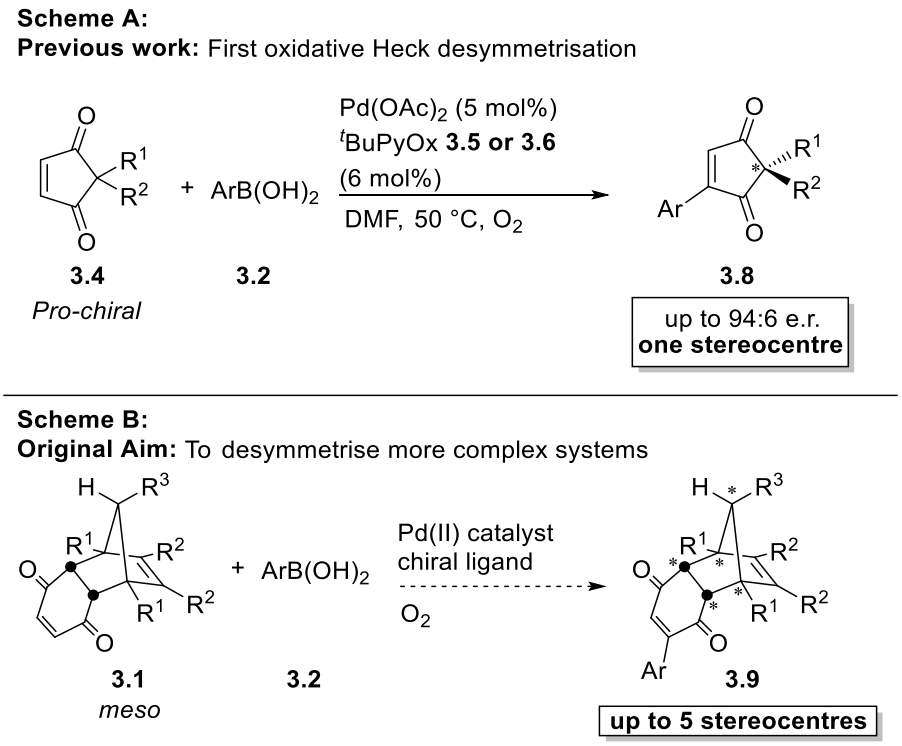
3.1 Introduction

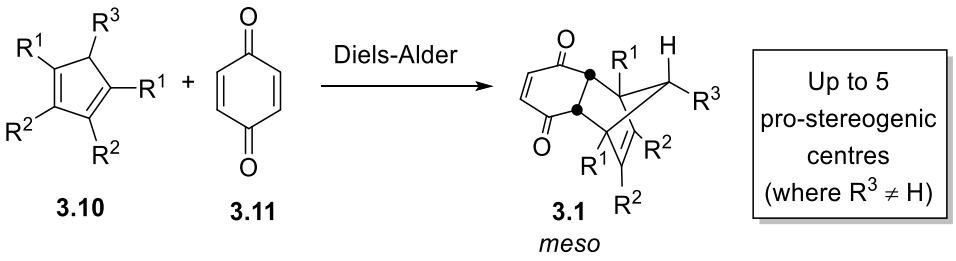
3.1.1 Background

The Lee group has demonstrated how powerful Pd(II)-catalysed oxidative Heck reactions can be used for desymmetrising difficult cyclic substrates. In past work and in Chapter 2, the successful desymmetrisation of 2,2-disubstituted cyclopentenediones **3.4** (Scheme 3.1A) was discussed.[1, 2] In these instances one pro-stereogenic centre was desymmetrised by an oxidative Heck coupling reaction. Next, we wanted to increase the challenge and difficulty by aiming to desymmetrise cyclic systems with multiple pro-stereogenic centres, utilising a Pd(II)-catalysed oxidative Heck approach (Scheme 3.1B).



Scheme 3.1: Original aim to apply Pd(II)-catalysed oxidative Heck chemistry to more complex system **3.1**

Meso-polycyclic cyclohexenediones **3.1** are easily accessed through a Diels-Alder reaction of *p*-benzoquinone **3.11** and a symmetric cyclopentadiene **3.10** (Scheme 3.2). *Meso*-polycyclic cyclohexenediones **3.1** contain at least four pro-stereogenic centres and would therefore be excellent candidates for desymmetrisation reactions. However, to the best of our knowledge this area is underdeveloped with respect to desymmetrisation *via* a coupling reaction. Therefore, developing an efficient desymmetrisation protocol of these Diels-Alder adduct motifs **3.1** (e.g. Scheme 3.1B) would be very interesting. Furthermore, a lot of complexity would be generated within one simple coupling reaction.



Scheme 3.2: Diels-Alder reaction to synthesise **3.1**

Meso-polycyclic cyclohexenediones **3.1** are often important precursors within the synthesis of natural products and biologically active compounds.[3-6] Therefore, developing an efficient protocol for desymmetrising these molecules would be synthetically beneficial for potentially improving synthetic routes in total syntheses, and widening the cache of reactions available.

In addition, *meso*-polycyclic cyclohexenediones **3.1** and oxidised polycyclic benzoquinone derivatives **3.12** have been shown to be effective ligands in platinum-catalysed hydrosilylation reactions (Figure 3.1A).[7] On a different note, but still somewhat related, Bäckvall and co-workers have documented the use of chiral *p*-benzoquinone derivatives **3.13** as ligands for enantioselective alkoxylation reactions

(Figure 3.1B).[8, 9] Therefore, taking inspiration from the above publications, accessing desymmetrised polycyclic cyclohexenediones **3.9** and oxidising to the corresponding chiral benzoquinone **3.14** (Scheme 3.3) could be very useful for furnishing a potentially interesting new chiral ligand class.

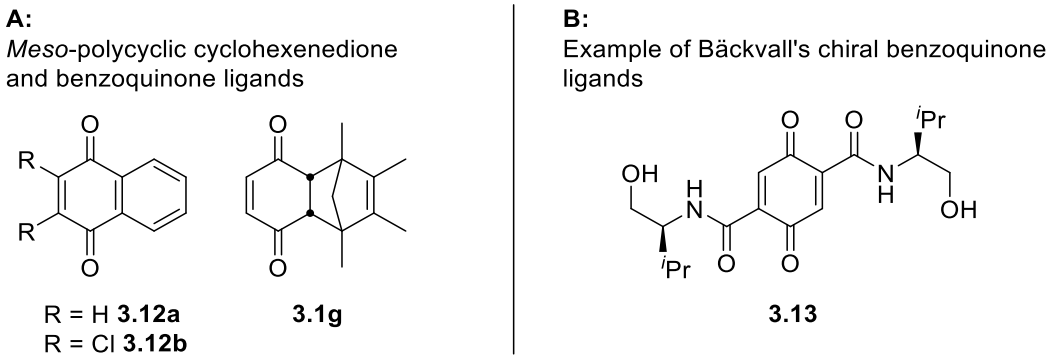
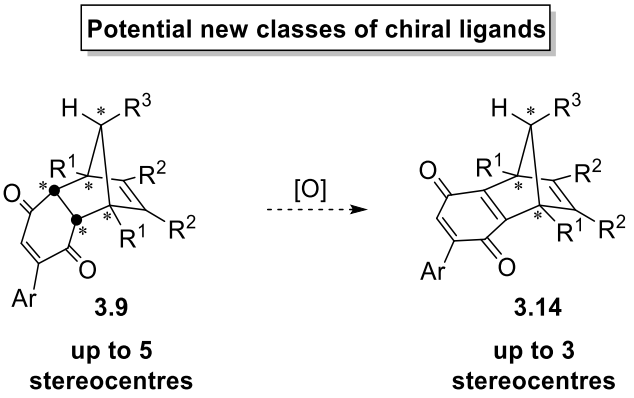


Figure 3.1: A: *Meso*-polycyclic cyclohexenedione and benzoquinone ligands[7]
B: Chiral benzoquinone ligand developed by Bäckvall *et al.*[9]



Scheme 3.3: Potential new class of interesting chiral ligand

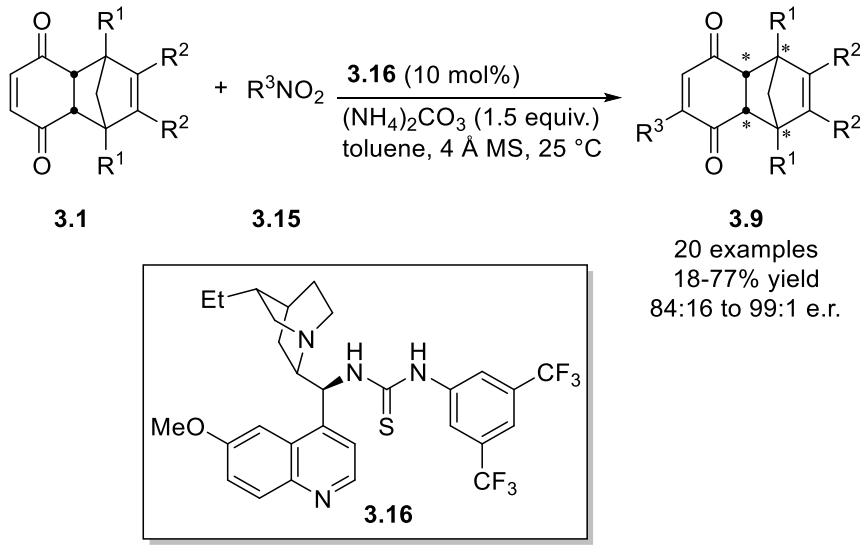
3.1.2 Desymmetrisation Reactions of *meso*-Polycyclic Cyclohexenediones

As mentioned in Section 3.1.1, despite m*eso*-polycyclic cyclohexenediones **3.1** being excellent candidates for desymmetrisation reactions, this remains an underdeveloped area of chemistry with respect to coupling reactions. While not the focus of the discussions within this chapter, there are a few reports of *meso*-Diels-Alder adducts **3.1**

being desymmetrised *via* selective asymmetric hydrogenation of a ketone to the alcohol.[10-12]

To the best of our knowledge, there is only one study focusing on the desymmetrisation of m*eso*-polycyclic cyclohexenediones **3.1** *via* a coupling reaction. During the course of our investigations into the Pd(II)-catalysed desymmetrisation of **3.1**, Mukherjee and co-workers published an organocatalysed desymmetrisation of the same types of compounds **3.1**.[13] They demonstrated that organocatalyst **3.16** could be employed in an addition/elimination reaction with nitroalkyls **3.15** to desymmetrise **3.1** and furnish coupled product **3.9** in good yields and excellent e.r.s (Scheme 3.4). An adequate m*eso*-polycyclic cyclohexenedione **3.1** scope was carried out but the nitroalkyl **3.15** scope was limited; nitro alkyls and esters coupled in good yields but benzylic and vinylic nitroalkyls struggled to react well.

It would, therefore, still be highly relevant and useful to develop a desymmetrisation reaction for **3.1** with complementary scope of R^3, as well as to offer a more environmentally benign alternative to the toxic nitroalkanes **3.15** used in Scheme 3.4.

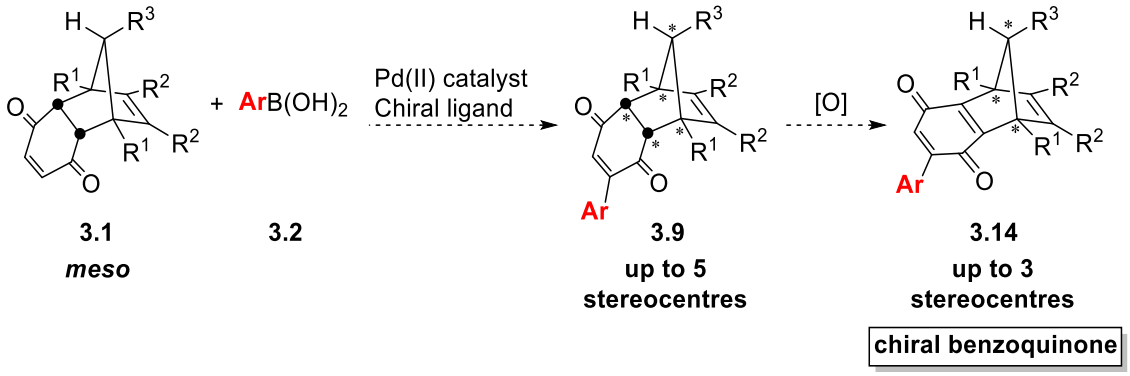


Scheme 3.4: Organocatalytic approach to desymmetrising **3.1**

3.2 Project Aims

The desymmetrisation of *meso*-polycyclic cyclohexenediones **3.1** has been an underdeveloped area, especially *via* a coupling reaction. We, therefore aimed to address this by developing a Pd(II)-catalysed oxidative Heck desymmetrisation reaction of Diels-Alder adducts **3.1** with boronic acids **3.2** (Scheme 3.5). If successful, this would constitute a novel application of oxidative Heck chemistry to generate a very complex product from a simple starting material **3.1**, where up to five stereocentres could be desymmetrised in one reaction.

In addition, we also aimed to investigate oxidising desymmetrised oxidative Heck product **3.9** to the chiral benzoquinone **3.14**, as a potentially efficient route to a new class of chiral ligands (Scheme 3.5).



Scheme 3.5: Original project aims: to develop a novel Pd(II)-catalysed reaction to desymmetrise multiple stereocentres in one reaction

3.3 Optimisation

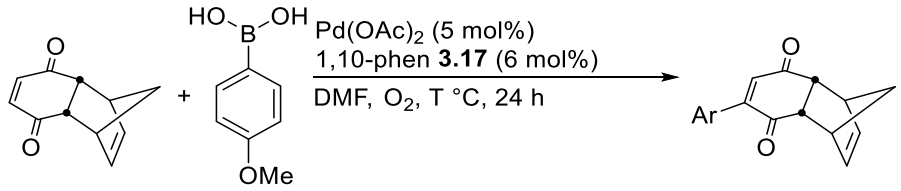
3.3.1 Initial Optimisation Studies with Diels-Alder Adduct 3.1a

3.3.1.1 Racemic coupling studies

As a starting point for desymmetrising molecules with multiple stereocentres, we aimed to develop racemic oxidative Heck coupling conditions of Diels-Alder adduct **3.1a** and *p*-methoxyphenyl boronic acid **3.2a**. The racemic product was required to establish chiral stationary phase HPLC separating conditions, to allow the recording of the enantiomeric ratio of the enantioenriched products.

We initiated our studies using previously established oxidative Heck coupling conditions within the Lee group: $Pd(OAc)_2$ (5 mol%), 1,10-phenanthroline **3.17** (5 mol%) in DMF in the presence of molecular oxygen. Starting with 70 °C (Table 3.1, entry 4), the optimised racemic coupling temperature in our previous work,[1] we only observed a complex mixture by ^{1}H NMR analysis of the crude reaction mixture and evidence of *p*-benzoquinone **3.11,** suggesting that retro-Diels-Alder had occurred. Unfortunately, lowering the reaction temperature did not promote any coupling reaction between **3.1a** and boronic acid **3.2a** either (entries 1-3). The chiral (*S*)-PyOx ligands that were planned to be used during our enantioselective studies also failed to furnish the desired coupled product, in this instance ^{t}BuPyOx **3.5** (entry 5). Presumably, due to leaving the reaction for an extended period of 3 days, evidence of retro-Diels-Alder reaction was visible in the crude reaction mixture.

Table 3.1: Attempted coupling with Diels-Alder adduct **3.1a**



3.1a 0.1 mmol | **3.2a** 2.5 equiv. | **3.9aa**

Entry	Temp (°C)	Yield (%)[a]	
		3.9aa	**3.1a**
1	rt	-	60
2	30	-	67
3	40	-	64
4	70	-[d]	n.d.[c,d]
5[b]	40	-	53

[a] Yield determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as internal standard, [b] Reaction with optimised enantioselective conditions (A), using $Pd(OAc)_2$ (5 mol%), ^{t}BuPyOx **3.5** (6 mol%), DMF, O_2 at 40 °C for 72 h. [c] Not determined. [d] Complex mixture.

3.3.1.2 Rationalisation of reactivity

As Diels-Alder adduct **3.1a** was not reacting to form **3.9aa** and with predominantly unreacted **3.1a** remaining, we hypothesised that the presence of the di-substituted alkene was responsible for the lack of reactivity. *Meso*-polycyclic cyclohexenedione **3.1a** is a bicyclic molecule containing an enedione and a di-substituted alkene. It was thought **3.1a** might be behaving as a diene ligand and chelating to the Pd(II) catalyst through the enedione and the alkene functionalities, thus affecting catalysis.

In order to obtain more information, we carried out ^{1}H NMR studies. We compared the alkene signals of a solution of Diels-Alder adduct **3.1a** and a 1:1:1 mixture of $Pd(OAc)_2$:^{t}BuPyOx **3.5**:**3.1a**. A slight shift in the alkene signals was observed which

may suggest that **3.1a** is chelating as a diene ligand (Figure 3.2). A 2D DOSY (Diffusion Ordered NMR Spectroscopy) experiment was also carried out on the 1:1:1 mixture. This showed that a large molecular weight complex had formed in the region of the $Pd(OAc)_2$/^{t}BuPyOx **3.5** complex signals, but there was also something much smaller in the mixture around the region of the free Diels-Alder adduct **3.1a**. This does not rule out indefinitely that **3.1a** is not acting as a diene ligand. It just suggests that if the Pd(II)/diene **3.1a** complex is forming, it is shorter lived than the NMR time scale. We also attempted to grow a crystal of the 1:1:1 **3.1a**:$Pd(OAc)_2$:^{t}BuPyOx **3.5** mixture but to no avail.

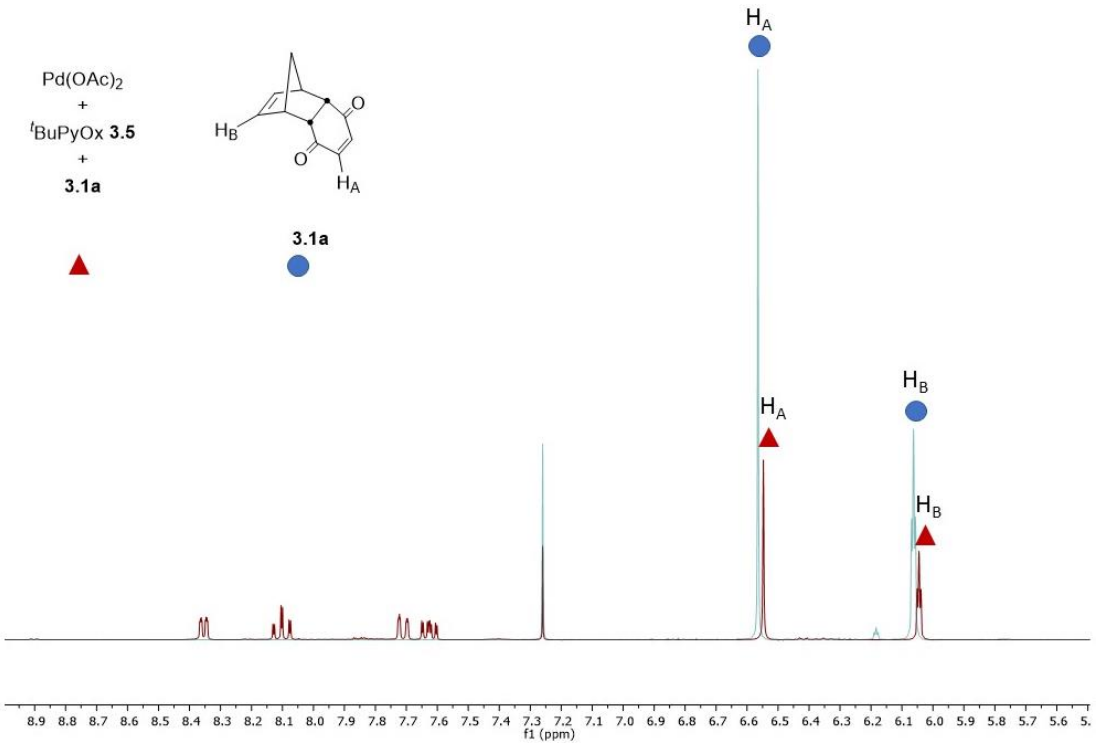


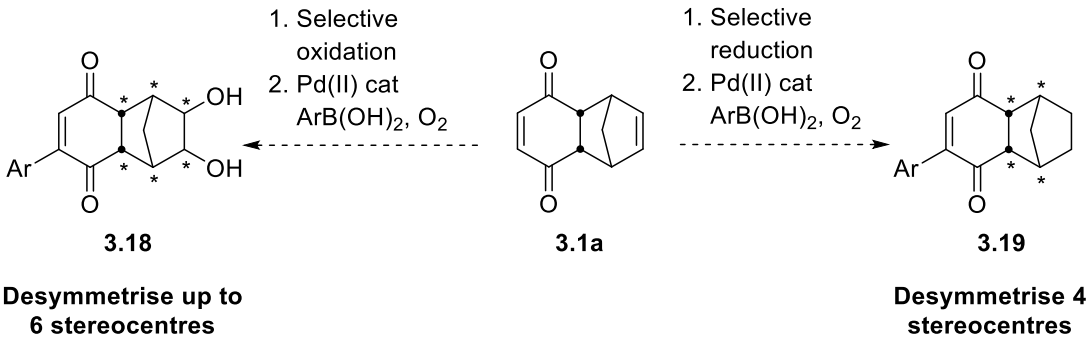
Figure 3.2: ^{1}H NMR study of cyclopentadiene Diels-Alder adduct **3.1a**

Overall, this evidence neither proves nor disproves our hypothesis that **3.1a** is behaving as a diene ligand under these Pd(II)-catalysed coupling conditions. We therefore sought other methods to prove our theory.

3.3.3.3 Selective alkene functionalisation of Diels-Alder adduct 3.1a

In an attempt to overcome the potential effect of a di-substituted alkene in Diels-Alder adduct **3.1a** on catalysis, we attempted to selectively react the di-substituted alkene over the alkene of the enedione (Scheme 3.6). By carrying out a selective alkene reduction or oxidation, the di-substituted alkene would no longer be present to interfere with catalysis whilst the enedione would still available for coupling. Furthermore, depending on the oxidation method selected, it could result in up to six contiguous stereocentres being desymmetrised in one oxidative Heck coupling reaction.

Several reduction and oxidation methods therefore were attempted, including hydrogenation (Rh/C, Pd/C, Adams' catalyst, Lindlar catalyst with various levels of poisoning, transfer hydrogenation),[14-18] Upjohn dihydroxylation and epoxidation.[19-21] Unfortunately, no method successfully furnished the compounds we desired, as the more electron-deficient alkene of the enedione would also undergo reduction or oxidation is all cases.

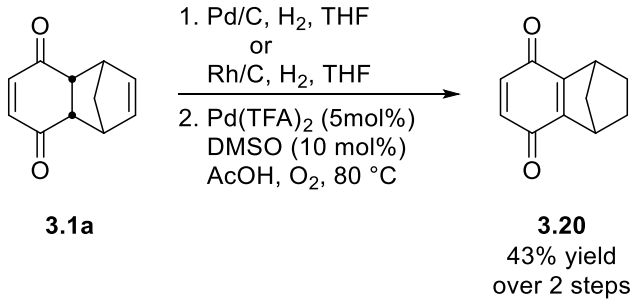


Scheme 3.6: Planned selective reductions and oxidations of Diels-Alder adduct **3.1a**

In our efforts to selectively hydrogenate the di-substituted alkene over the enedione in Diels-Alder adduct **3.1a**, we were instead able to fully reduce **3.1a** (Scheme 3.7). We then successfully synthesised the corresponding *meso*-benzoquinone **3.20,** through a subsequent Stahl oxidation (Scheme 3.7).[22] Interestingly, we were able to desymmetrise

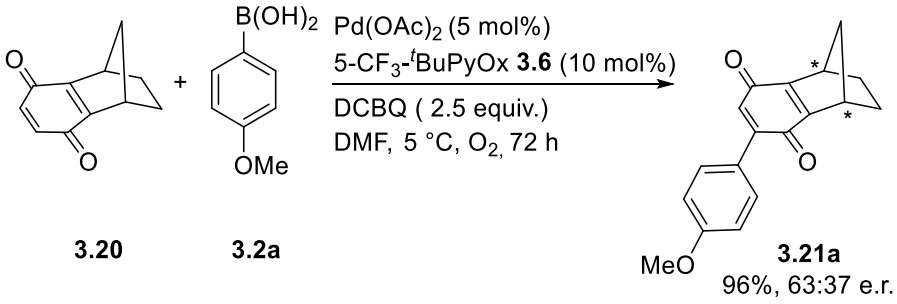
3.20 through an oxidative Heck reaction to coupled benzoquinone **3.21a** in excellent yield (96%, Scheme 3.8). Unfortunately, however, we were only able to do so in poor enantioselectivities (63:37 e.r.). DCBQ (1,4-dichlorobenzoquinone) was required for good yield; it is required to either re-oxidise Pd(0)→Pd(II), or if the benzoquinone product **3.21a** is oxidising the catalyst from Pd(0)→Pd(II), DCBQ could then be used to oxidise the corresponding hydroquinone back to the coupled benzoquinone product **3.21a**.

As much as this would have been a very efficient route to the synthesis of chiral benzoquinones, we were not able to improve upon 63:37 e.r. and this route was thus abandoned.[v] This work was carried out in collaboration with summer student W. Daul.[‡23]



Scheme 3.7: Route to *meso*-benzoquinone **3.20**

[v] **3.20** is more planar, in comparison to Diels-Alder adducts **3.1b-i** which are more puckered (see Section 3.1.4). This possibly results in either face (*endo*- or *exo*-face) of **3.20** being equally available for association to the chiral Pd(II) catalyst and therefore, may explain the low enantioselectivity in the synthesis of **3.21a** (Scheme 3.8).



Scheme 3.8: Desymmetrisation of *meso*-benzoquinone **3.20**

3.3.2 Optimisation Studies with Diels-Alder Adduct 3.1b

All our efforts to develop a Pd(II)-catalysed desymmetrisation approach of Diels-Alder adduct **3.1a** have been unsuccessful. Suspecting the presence of a di-substituted alkene to be affecting catalysis, we next decided to investigate the coupling of Diels-Alder adducts where the alkene would be tetra-substituted, which would hopefully block the substrate from potentially behaving like a diene ligand and prove our hypothesis.

We decided to try to desymmetrise Diels-Alder adduct **3.1b**, which contains a tetra-substituted alkene, and is easily synthesised from commercially available 1,2,3,4-tetrachloro-5,5-dimethoxycyclopentadiene **3.10b** and *p*-benzoquinone **3.11**. As before (Section 3.3.1), our investigations started with previously established racemic oxidative Heck conditions within the Lee group, coupling Diels-Alder adduct **3.1b** with *p*-methoxyphenyl boronic acid **3.2a**. To our surprise, no oxidative Heck product was obtained but conjugate addition product **3.3ba** was furnished exclusively in 74% yield and excellent diastereoselectivity (>20:1 d.r.) (Table 3.2, entry 1). Despite not being the result we originally envisaged, this result does provide more evidence that the less substituted di-substituted alkene in Diels-Alder adduct **3.1b** could be having an effect on catalysis in Section 3.3.1.

Although we originally aimed to develop an oxidative Heck desymmetrisation reaction, the development of the conjugate addition desymmetrisation reaction instead would also be synthetically interesting. Not only would a Pd(II)-catalysed conjugate addition be novel, but it would allow for even more complexity to be generated within one reaction. A new stereocentre is now being created along with several pro-stereogenic centres being desymmetrised in one reaction. Furthermore, to the best of our knowledge, a Pd(II)-catalysed conjugate addition has not been employed in an intermolecular desymmetrisation reaction, let alone being employed in desymmetrising multiple stereocentres in one reaction.[vi, 24, 25] Therefore, we decide to pursue the development of a Pd(II)-catalysed conjugate addition desymmetrisation reaction.

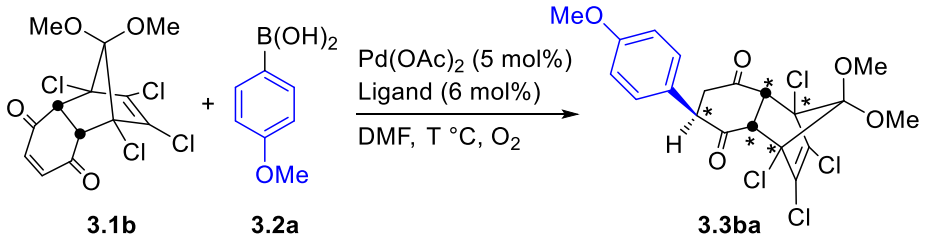
Now with the revised aim of developing a new conjugate addition reaction instead, we proceeded to screen chiral ligands, focusing on (*S*)-PyOx ligands **3.5, 3.6** and **3.7** (Figure 3.3). Increasing the reaction temperature to 30, 40 or 50 °C with ^{t}BuPyOx **3.5** improves yield (Table 3.2, entries 2, 3, 5), however, it also resulted in a decrease in enantioselectivity. Increasing the reaction time from 24 h to 72 h improves the yield with ^{t}BuPyOx **3.5** as ligand to 80% yield and an e.r. of 92:8. Neither 5-CF_3-^{t}BuPyOx **3.6** nor 4-CF_3-^{t}BuPyOx **3.7** as ligand furnished coupled product **3.3ba** in a yield that surpasses that of ^{t}BuPyOx **3.5** and therefore, no enantiomeric ratios were recorded (entries 7 and 8). Switching the solvent from DMF to less ligating DMA also did not positively affect the reaction in terms of yield (entry 9).

The proposed conjugate addition mechanism does not require oxygen (see Chapter 1, Section 1.2.6, Scheme 1.26 and Section 1.4) as the palladium oxidation state in the catalytic cycle is isohypsic at Pd(II).[26, 27] However, when the reaction was run under air

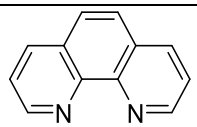
[vi] Pd(II)-catalysed conjugate addition cyclisation reactions have been employed in intramolecular desymmetrisation reactions but not utilising aryl boronic acids as coupling partners.[24, 25]

instead of O_2 we observed a decrease in yield (Table 3.2, entry 4 vs. entry 3). If any side product formation does occur, even if only in trace amounts (*i.e.* homocoupling and phenol formation from the associated boronic acid), this would take the catalyst oxidation state to Pd(0) through reductive elimination.[28] It was postulated that without enough molecular oxygen present in the reaction, the catalyst cannot reoxidise to Pd(II) and transmetallation of the boronic acid cannot continue to occur. Therefore, to improve the yield and reproducibility of the reaction, we opted to carry all future reactions under an atmosphere of molecular oxygen, unless otherwise stated.

Table 3.2: Racemic and enantioselective conjugate addition optimisation



3.1b **3.2a** **3.3ba**

Entry	Ligand	Time (h)	Temp (°C)	Yield (%)[a, b]	e.r.[d]
1	 **3.17**	24	r.t.	74	-
2	^{t}BuPyOx **3.5**	24	30	16	93:7
3	^{t}BuPyOx **3.5**	24	40	25[e]	92:8
4[c]	^{t}BuPyOx **3.5**	24	40	16	n.d.[g]
5	^{t}BuPyOx **3.5**	24	50	63	85:15
6	^{t}BuPyOx **3.5**	72	30	80	92:8
7	4-CF$_3$^{t}BuPyOx **3.7**	72	30	14[d]	n.d.[g]
8	5-CF$_3$^{t}BuPyOx **3.6**	72	30	trace	n.d.[g]
9[f]	^{t}BuPyOx **3.5**	72	30	35[d]	n.d.[g]

[a] Isolated yield. [b] D.r. >20:1. [c] Carried out in air. [d] E.r. determined by CSP-HPLC. [e] Yield determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene. [f] DMA as solvent [g] N.d. = not determined

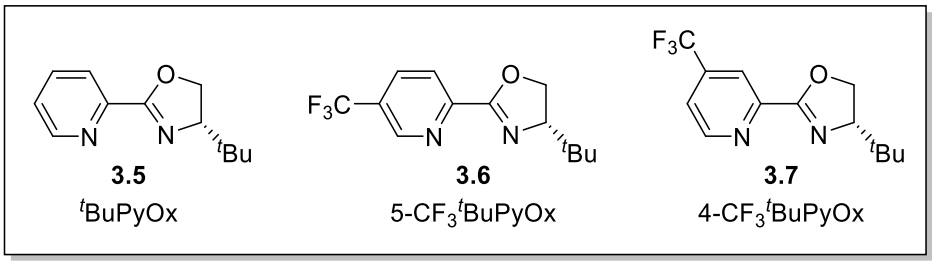
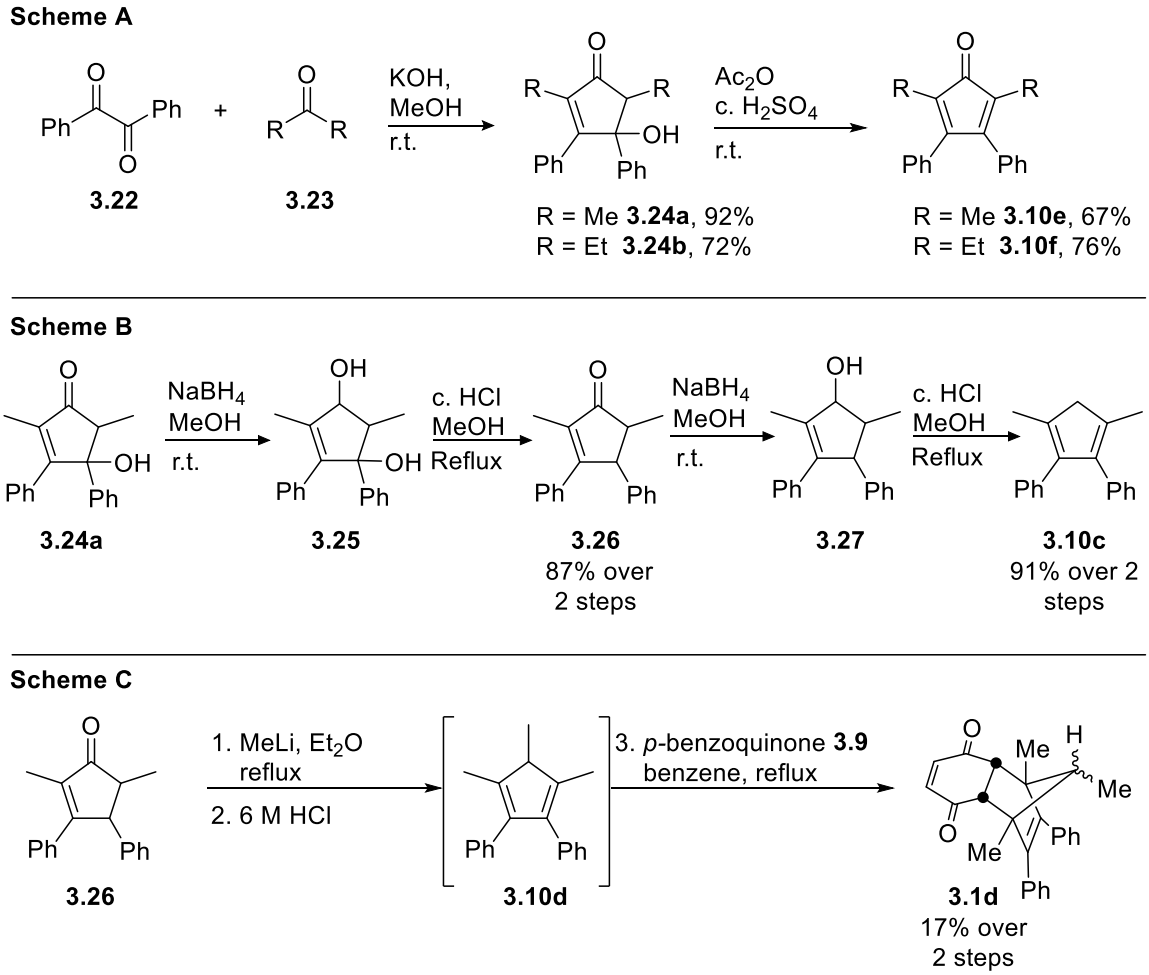


Figure 3.3: (*S*)-*t*BuPyOx ligands

3.4 Diels-Alder Adduct Scope

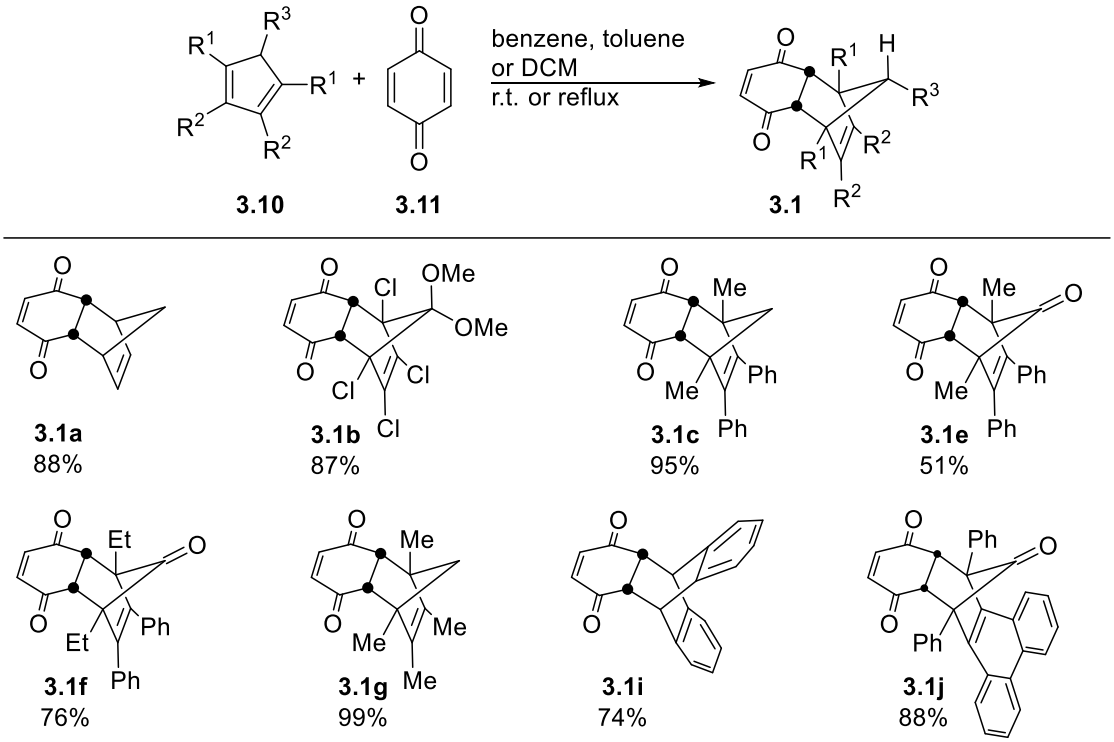
3.4.1 Synthesis of Symmetrical Cyclopentadienes 3.10 and their Diels-Alder Adducts 3.1

Having established that a tetra-substituted alkene is necessary in the *meso*-polycyclic cyclohexenediones **3.1** in order to get a successful coupling reaction, we proceeded to synthesise a series of tetra-substituted Diels-Alder adducts **3.1**. Most of the tetra-substituted symmetrical cyclopentadienes **3.10** required for the Diels-Alder reaction were commercially available. The non-commercially available cyclopentadienes were all easily synthesised from a similar starting point: an intermolecular aldol condensation reaction followed by an intramolecular aldol cyclisation reaction with a symmetric ketone **3.23** and benzil **3.22** (Scheme 3.9A).[29] A dehydration reaction could be performed to access cyclopentadienones **3.10e** (R^1 = Me) and **3.10f** (R^1 = Et) from **3.24a** and **3.24b** respectively (Scheme 3.9A).[30] Alternatively, a series of ketone reductions and dehydrations could be performed to access cyclopentadiene **3.10c** (Scheme 3.9B).[29] Lastly, methylation of **3.26** with MeLi furnished 1,2,5-trimethyl-3,4-diphenylcyclopentadiene **3.10d** which was immediately subjected to Diels-Alder conditions (due to the diene being prone to dimerization) to yield **3.1d** in 7:1 d.r. (Scheme 3.9C).[13]



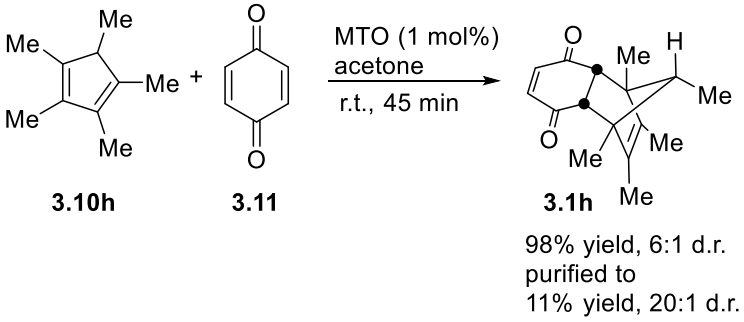
Scheme 3.9: Synthetic route to symmetrical cyclopentadienes **3.10**

The synthesis of the *meso*-Diels-Alder adducts **3.1** was easily carried out (Scheme 3.10). Simply stirring symmetrically substituted cyclopentadiene **3.10** with *p*-benzoquinone **3.11** together in benzene, toluene or DCM at either room temperature or under reflux was suitable for furnishing *meso*-Diels-Alder adduct **3.1** in generally very good yields (Scheme 3.10, 51-99 %) (see Section 3.9 for experimental details).



Scheme 3.10: General scheme for the preparation of *meso*-Diels-Alder adducts **3.1**

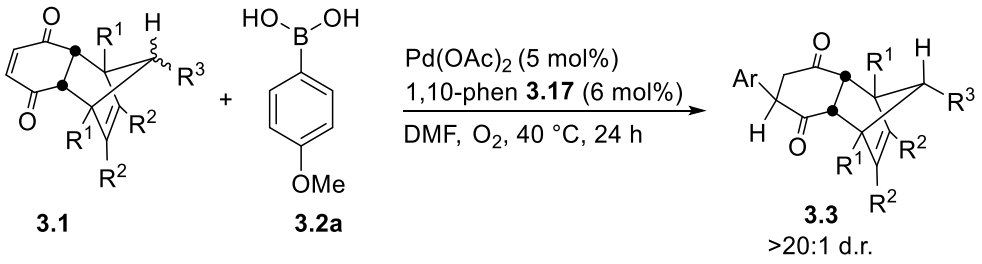
The Diels-Alder reaction generated diastereomers where R^3 in cyclopentadiene **3.10** is not a hydrogen. This has already been documented above to be the case for the synthesis of Diels-Alder adducts **3.1d** (Scheme 3.9, Scheme C). Unfortunately, **3.1d** could not be purified to improve the diastereomeric ratio any further, so it was instead subjected to conjugate addition conditions as a mixture of diastereomers (7:1 d.r.). The Diels-Alder adduct with 1,2,3,4,5-pentamethylcyclopentadiene **3.10h** was also synthesised as a 6:1 mixture of diastereomers (Scheme 3.11). A literature preparation was followed which claimed to give >20:1 d.r. of Diels-Alder adduct **3.1h** using methyltrioxorhenium (MTO) as a catalyst.[31] However, we were unable to reproduce these results. Fortunately, a portion of **3.1h** could be purified to 20:1 d.r. to be used for our optimised conjugate addition conditions.



Scheme 3.11: Synthesis of *meso*-Diels-Alder adduct **3.1h**

3.4.2 Racemic *meso*-Diels-Alder Adduct Scope

As an enantioselective desymmetrisation reaction is the focus of our study, an in-depth discussion of the racemic conjugate addition reaction is not included in this chapter. A general racemic palladium(II)-catalysed conjugate addition procedure was developed in order to synthesise the racemic conjugate addition products (Table 3.2, entry 1 and Scheme 3.12). All racemic conjugate addition products were synthesised in >20:1 diastereomeric ratio and for the sole purpose of obtaining chiral stationary phase HPLC separating conditions. For full details of racemic conjugate addition conditions, please refer to the experimental details in Section 3.9.

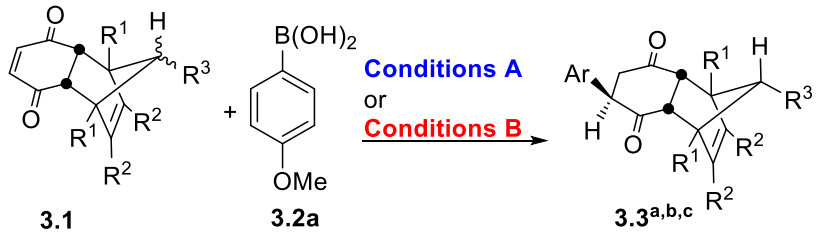


Scheme 3.12: Racemic conjugate addition reaction conditions

3.4.3 Enantioselective *meso*-Diels-Alder Adduct Scope

For clarity, Table 3.3 shows the best overall results from the Diels-Alder adduct scope. In order to overcome some problems in the enantioselective conjugate addition reaction, two sets of optimised conditions had to be developed: conditions A and conditions B. Conditions A are the previously optimised conditions established in Section 3.3.2. Overall, a wide Diels-Alder adduct **3.1** scope study has been successfully carried out. In Section 3.4.3.1, a full commentary on the application of conditions A in the enantioselective *meso*-Diels-Alder adduct **3.1** scope is presented. Detailed discussions on the necessity and application of conditions B to the enantioselective *meso*-Diels Alder adduct **3.1** scope will be covered in Sections 3.4.3.2, 3.4.3.3 and 3.4.3.4.

Table 3.3: Overall results of the Diels-Alder adduct scope

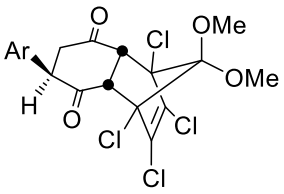


3.1 **3.2a** **3.3**[a,b,c]

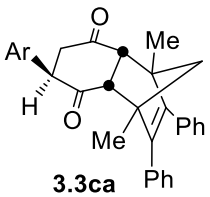
0.1 mmol 2.4 equiv. Ar = *p*-$MeOC_6H_4$-

Conditions A:
$Pd(OAc)_2$ (5 mol%)
^{t}BuPyOx **3.5** (6 mol%)
DMF, O_2, 40 °C, 72 h

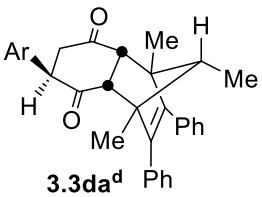
Conditions B:
$Pd(TFA)_2$ (5 mol%)
(*S*)-PyOx **3.6** or **3.7** (6 mol%)
DCE, 40 °C, 72 h



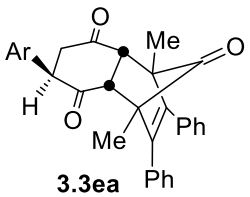
A: 80%, 92:8 e.r.
Ar = *p*-$MeOC_6H_4$- **3.3ba**
A: 65%, 90:10 e.r.
Ar = *p*-OHC_6H_4- **3.3bd**



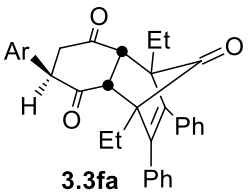
3.3ca
A: 70%, 97:3 e.r.



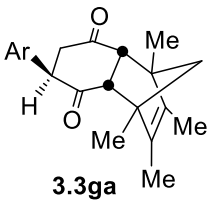
3.3da[d]
A: 73%, 97:3 e.r.



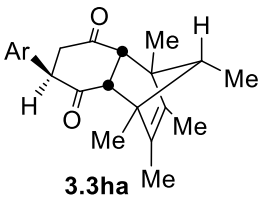
3.3ea
A: 68%, 94:6 e.r.



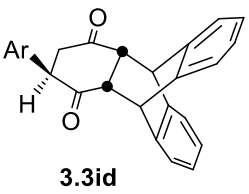
3.3fa
A: 0.1 mmol
72%, 92:8 e.r.
A: 1.0 mmol[g]
60%, 93:7 e.r.



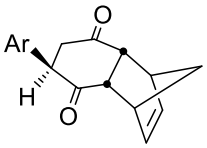
3.3ga
A: 43%,[f] 97:3 e.r.
B: 68%, 95:5 e.r.



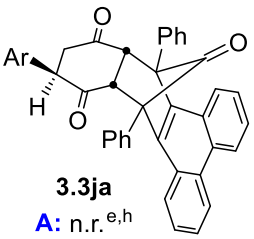
3.3ha
B: 64%, 95:5 e.r.



3.3id
B: 65%, 85:15 e.r.
Ar = *p*-OHC_6H_4-



3.3aa
A: n.r.[e]



3.3ja
A: n.r.[e,h]

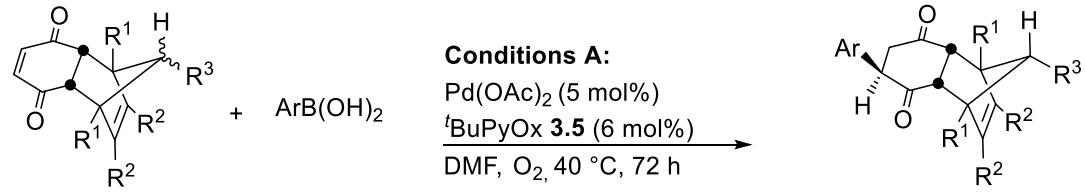
[a] Isolated yield. [b] >20:1 D.r., determined by ^{1}H NMR analysis. [c] Enantiomeric ratio determined by CSP-HPLC. [d] Carried out on 0.05 mmol scale, $Pd(OAc)_2$ (10 mol%), ^{t}BuPyOx **3.5** (11 mol%). [e] No reaction. [f] ~90% clean. Carried out with $Pd(OAc)_2$ (10 mol%) and ^{t}BuPyOx **3.5** (11 mol%). [g] 1.0 mmol Scale up. [h] Conditions A with 1,10-phen **3.17** (6 mol%).

3.4.3.1 Enantioselective *meso*-Diels-Alder adduct scope with conditions A

With optimised Pd(II)-catalysed enantioselective conjugate addition reaction conditions developed, we sought to carry out a Diels-Alder adduct **3.1** substrate scope study (Table 3.4). The conjugate addition reaction was successfully achieved in >20:1 d.r. throughout and overall very good enantioselectivities were observed. Acetal protected ketone **3.1b** (see Scheme 3.10) reacted well with *p*-methoxyphenyl boronic acid **3.2a**, as was already observed during the optimisation in Section 3.3.2 (**3.3ba** 80%, 92:8 e.r.). Furthermore, **3.1b** also proceeded well with *p*-hydroxyphenyl boronic acid **3.2d** to give a 65% yield of **3.3bd** and an e.r. of 90:10. However, more pleasingly, unprotected ketone substrates **3.1e** and **3.1f** also coupled in good yields and e.r.s to yield **3.3ea** (68%, 94:6 e.r.) and **3.3fa** (72%, 92:8 e.r.). A scale up was also carried out at 1.0 mmol scale to furnish **3.3fa**. There was a slight decrease in isolated yield (from 72% to 60%) at the larger scale but enantioselectivity of coupled product **3.3fa** was maintained (93:7 e.r.). Dimethyl-diphenyl substrate **3.1c**, where there is no substitution at the top of the bridge, was desymmetrised in a very good 97:3 e.r. and 70% isolated yield.

Trimethyl-diphenyl substrate **3.1d** (see Scheme 3.9C) was subjected to the conjugate addition conditions as a 7:1 mixture of diastereomers. The enantioselective conjugate addition reaction itself is diastereoselective. Therefore, the respective conjugate addition products of each diastereomer of starting material **3.1d** were diastereomerically pure. The conjugate addition product **3.3da** of the major diastereomer with respect to the starting material was purified by silica gel chromatography in 73% yield and a very good e.r. of 97:3. Furthermore, the structure of **3.3da** was confirmed by 2D NOESY NMR (Figure 3.4). Unfortunately, we were not able to obtain a pure enough sample of the conjugate addition product of the minor diastereomer with respect to the starting material to establish the enantioselectivity.

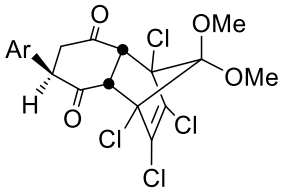
Table 3.4: *Meso*-Diels-Alder adduct scope with conditions A



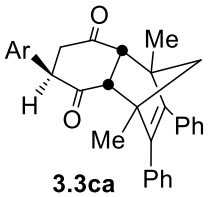
3.1a
0.1 mmol

3.2a
Ar = *p*-$MeOC_6H_4$-
2.4 equiv.

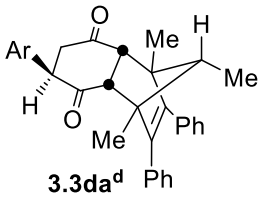
3.3[a,b,c]
Ar = *p*-$MeOC_6H_4$-



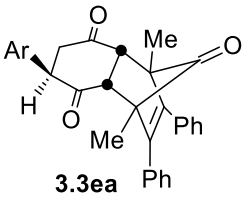
Ar = *p*-$MeOC_6H_4$- **3.3ba**
80%, 92:8 e.r.
Ar = *p*-$MeOC_6H_4$- **3.3bd**
65%, 90:10 e.r.



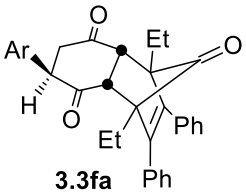
3.3ca
70%, 97:3 e.r.



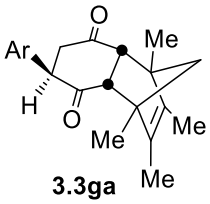
3.3da[d]
73%, 97:3 e.r.



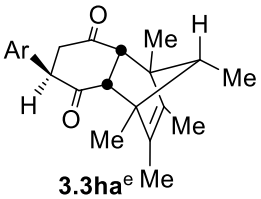
3.3ea
68%, 94:6 e.r.



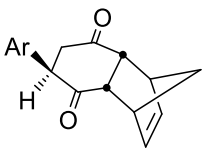
3.3fa
0.1 mmol
72%, 92:8 e.r.
1.0 mmol
60%, 93:7 e.r.



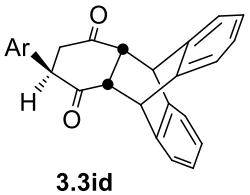
3.3ga
43%,[i] 97:3 e.r.



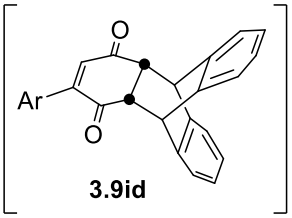
3.3ha[e]



3.3aa
n.r.[h]

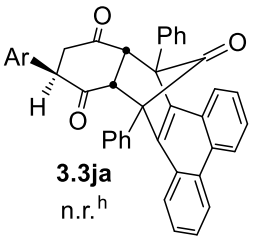


3.3id



3.9id

Ar = *p*-HOC_6H_4- 91:9[f] **3.9id**:**3.3id**
84:16 e.r.[g]



3.3ja
n.r.[h]

[a] Isolated yield. [b] >20:1 d.r., determined by ^{1}H NMR analysis. [c] Enantiomeric ratio determined by CSP-HPLC. [d] Carried out on 0.05 mmol scale, $Pd(OAc)_2$ (10 mol%), ^{t}BuPyOx **3.5** (11 mol%). [e] Substrate not tried under these reaction conditions. [f] NMR yield determined by ^{1}H NMR analysis with internal standard 1,3,5-trimethoxybenzene. [g] E.r. recorded of **3.3id.** [h] No reaction under racemic conditions so enantioselective conditions were not applied. [i] ~90% purity. Carried out with $Pd(OAc)_2$ (10 mol%) and ^{t}BuPyOx **3.5** (11 mol%)

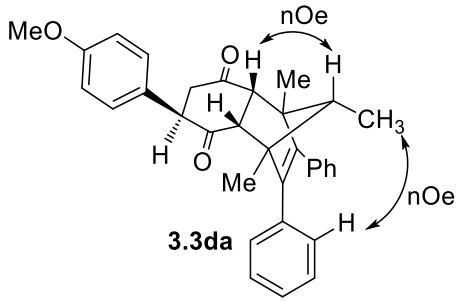


Figure 3.4: nOe Observed in 2D NOSY NMR of **3.3da**

These optimised conditions could be applied to Diels-Alder adduct **3.1g** (see Scheme 3.10), however, there is a significant decrease in yield (43%, ~90% pure) of **3.3ga**, albeit with excellent enantioselectivity (97:3 e.r.). Concerned that these conditions were not optimal for methyl substituted alkene substrates (**3.1g** and **3.1h**, see Scheme 3.10 and 3.11 respectively), we did not want to subject what little we had purified of **3.1h** to these conditions. Further optimisation of conditions was carried out on these substrates, which is detailed in Section 3.4.3.2.

Another interesting substrate under these conditions was the Diels-Alder adduct of *p*-benzoquinone and anthracene. Upon reacting under optimised conditions A, we unexpectedly observed what we believed to be a 9% ^{1}H NMR yield of conjugate addition product **3.3id** and 91% yield *oxidative Heck* product **3.9id**. Further optimisation of reaction conditions was also carried out for the synthesis of **3.3id**, which is discussed in Section 3.4.3.3.

As observed in Section 3.3.1, the presence of a di-substituted alkene in **3.1a** is thought to be detrimental to the reaction (no **3.3aa** was observed, Table 3.4). Multiple attempts at developing conditions to improve the yield were carried out, however, none were successful. For further discussion see Section 3.3.1.

Lastly, Diels-Alder adduct **3.1j** (see Scheme 3.10), also did not successfully undergo racemic conjugate addition. However, this lack of reactivity is thought to be due to solubility issues. Even at elevated temperatures, **3.1j** would not dissolve in the reaction solution.

3.4.3.2 Development of optimised conditions B for methyl-substituted alkene substrates 3.1g and 3.1h

As seen in Section 3.4.3.1, some substrates did not react as successfully under enantioselective conditions A as we would have predicted. The racemic reaction did not give any indication that methyl-substituted alkene substrates **3.1g** and **3.1h** would struggle to undergo enantioselective conjugate addition under conditions A. Compounds **3.1g** and **3.1h** furnished **3.3ga** and **3.3.ha** in 77% and 86% yields respectively under racemic conditions. It should be noted that Diels-Alder adduct **3.1h** was reacted at a higher ligand and catalyst loading of 11/10 mol% respectively on a smaller scale (0.05 mmol) due to the scarcity of pure **3.1h**.

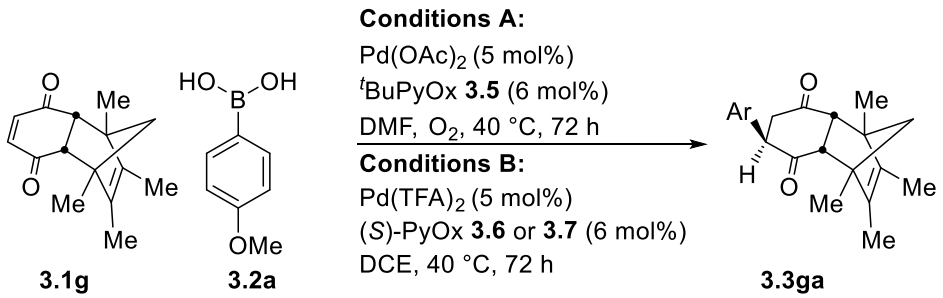
Under enantioselective conditions A, only 30% NMR yield was obtained of **3.3ga** from **3.1g**, which was only increased slightly by increasing catalyst and ligand loading to 10/11 mol% respectively (43% NMR yield). Furthermore, **3.3ga** could not be isolated pure (~90% pure) due to co-elution with unknown contaminants (Table 3.5, entries 1 and 2). Despite this, an excellent e.r. of 97:3 was recorded.

We were concerned that the optimised reaction conditions (conditions A) were not appropriate for all substrates in our investigations, especially tetramethyl-substituted **3.1g** and pentamethyl-substituted **3.1h**. Conditions A are typical oxidative Heck coupling conditions and therefore are perhaps not the best suited for achieving high conjugate addition yields across a wide range of substrates.[27] As discussed in Chapter 1, Section 1.4, Stoltz *et al.* have carried out several studies into Pd(II)-catalysed

enantioselective conjugate addition reactions on cyclic enones with excellent results. Therefore, we decided to take some inspiration from their reaction conditions to see if these conditions could improve the conjugate addition yield of substrates **3.1g** and **3.1h**.

By employing $Pd(TFA)_2$ (5 mol%), (*S*)-^{t}BuPyOx ligands **3.5** (6 mol%) in DCE as solvent (Conditions B), an improvement in yield is noted (Table 3.5, entry 1 vs. entry 9). It became apparent that the purity of the boron coupling source is more important under these new conditions. In Conditions A, the boronic acid could be used directly out of the bottle. On the other hand, with Conditions B, there is a preference for recrystallised aryl boronic acid **3.2** over the dehydrated aryl boroxine or the equilibrium mixture obtained straight from the bottle (entries 3-5). Using the aryl boronic acid **3.2a** furnished conjugate addition product **3.3ga** in 67% yield and 92:8 e.r., however, there was still 20% of starting material remaining. Unexpectedly, using molecular oxygen to aid catalytic turnover, resulted in a decreased yield (54% by ^{1}H NMR spectroscopy, entry 6). Meanwhile, increasing the catalyst and ligand loading to 10/11 mol%, respectively, also reduced yield, and an increased amount of homocoupling and phenol was observed in the crude ^{1}H NMR spectrum (entry 7). Portionwise addition of catalyst, ligand **3.7** and boronic acid **3.2a** did improve the yield to 72% (entry 8). Strangely, the enantioselectivity of the reaction decreased to 85:15 so portionwise addition was not considered viable. A ligand screen did produce positive results. The best ligand, 5-CF_3-^{t}BuPyOx **3.6,** did not improve on the yield but did gratifyingly boost the e.r. to 95:5 (entry 10).

Table 3.5: Development of optimised conditions B

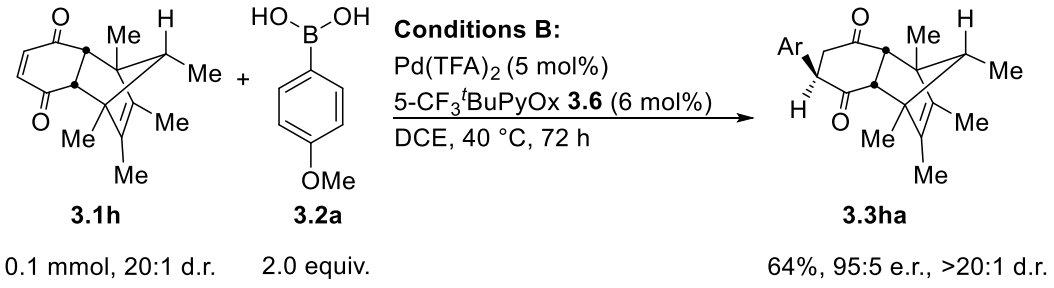


Entry	Conditions	Ligand	NMR Yield (%)[a] 3.1g:3.3ga	Isolated Yield (%) 3.3ga	e.r.[b]
1	A	^{t}BuPyOx **3.5**	20:30	-	-
2[c]	A	^{t}BuPyOx **3.5**	-:43	43[i]	97:3
3[d]	B	4-CF$_3$^{t}BuPyOx **3.7**	20:67	67	92:8
4[e]	B	4-CF$_3$^{t}BuPyOx **3.7**	30:42	-	-
5[f]	B	4-CF$_3$^{t}BuPyOx **3.7**	34:43	-	-
6[g]	B	4-CF$_3$^{t}BuPyOx **3.7**	22:54	-	-
7[c]	B	4-CF$_3$^{t}BuPyOx **3.7**	34:56	-	-
8[h]	B	4-CF$_3$^{t}BuPyOx **3.7**	12:74	72	85:15
9	B	^{t}BuPyOx **3.5**	24:61	61	90:10
10	B	5-CF$_3$^{t}BuPyOx 3.6	13:69	68	95:5

[a] Yield determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as internal standard. [b] E.r. determined by chiral stationary phase HPLC (CSP-HPLC). [c] Reaction carried out with Pd(OAc)$_2$ (10 mol%) and ^{t}BuPyOx **3.5** (11 mol%). [d] Recrystallised boronic acid. [e] Boronic acid straight from bottle. [f] Boroxine dehydrated from corresponding boronic acid under vacuum with a heat gun until all visible condensation is driven off. [g] Vial filled with O_2 before being tightly capped. [h] Portionwise addition of Pd(OAc)$_2$ (5 mol%), 4-CF$_3$^{t}BuPyOx **3.7** (6 mol%) and recrystallised boronic acid (1.5 equiv.) added at the start, then a further portion of each added after 24 h and left to stir for a further 48 h. [i] ~90% Purity.

Furthermore, these new optimised conditions (conditions B) were also successfully applied to pentamethyl Diels-Alder adduct **3.1h,** with an isolated yield of 67% of desymmetrised product **3.3ha**, an e.r. of 95:5 and >20:1 diastereomeric ratio (Scheme 3.13). The starting material was subjected to reaction conditions as a 20:1 mixture of

diastereomers but the reaction is diastereomerically selective, so the conjugate addition product **3.3ha** was successfully purified to >20:1 d.r.



Scheme 3.13: Application of conditions B to pentamethyl Diels-Alder adduct **3.1h**

3.4.3.3 Enantioselective conjugate addition with anthracene Diels-Alder adduct 3.1i under conditions B

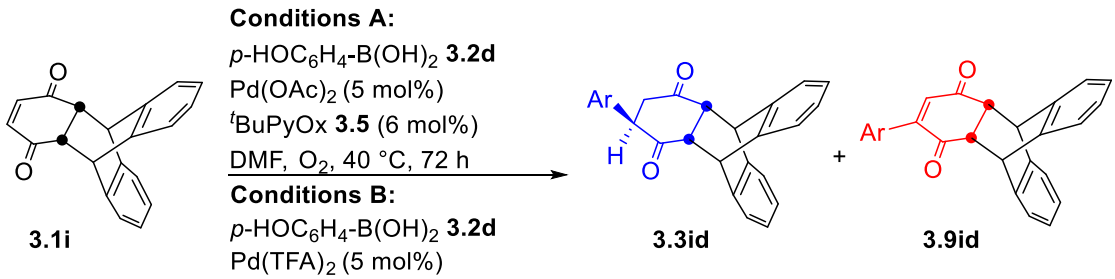
Under the application of optimised conditions A, anthracene Diels-Alder adduct **3.1i** behaved the least predictably, but the most interestingly. During our racemic investigations, it was the only Diels-Alder adduct which reacted to produce both the conjugate addition product **3.3i** and the oxidative Heck product **3.9i**, which are unfortunately not separable by column chromatography regardless of aryl boronic acid coupling partner used. Furthermore, it is the only substrate where we have been able to isolate the benzoquinone product. For further discussions of our racemic studies of anthracene Diels-Alder adduct **3.1i**, please refer to Appendix I.

For the enantioselective investigations, we found it necessary to change to *p*-hydroxyphenyl boronic acid **3.2d** as coupling partner instead of *p*-methoxyphenyl boronic acid **3.2a** in order to obtain chiral stationary phase HPLC separating conditions. Utilising conditions A, we observed a mixture of conjugate addition **3.3i** (9% NMR yield) and oxidative Heck **3.9i** (91% NMR yield) products (Table 3.6, entry 1). In an attempt to control the formation of conjugate addition product **3.3id** over oxidative Heck product **3.9id**, we ran the reaction under air instead of molecular oxygen, but this was

detrimental to the yield of both products (entry 2). Carrying out a ligand screen under conditions A also did not improve the selectivity between conjugate addition **3.3id** and oxidative Heck **3.9id** (entries 3 and 4). Strangely, as both reactions are thought to have the same enantio-determining step (for further discussions of mechanisms, see Chapter 1, Sections 1.4), the e.r. recorded for the oxidative Heck reaction was worse than that of the conjugate addition reaction (Table 3.6, entries 1, 3 and 4). Nevertheless, it should be noted that there may be some doubt over the e.r.s as **3.9id** was never isolated in pure form. We therefore sought means to selectively synthesise the conjugate addition product **3.3id.**

As conditions B had been successful with Diels-Alder adducts **3.1g** and **3.1h** (Section 3.4.3.2)**,** we hoped that they could also be employed to selectively form the conjugate addition product of anthracene Diels-Alder adduct **3.1i.** Pleasingly, this was the case with no oxidative Heck product **3.9id** visible in the crude reaction mixture. Carrying out a ligand screen under conditions B (Table 3.6, entries 5-7), showed the best ligand to be 4-CF_3-^{t}BuPyOx **3.7**, which furnished the desymmetrisation of anthracene Diels-Alder adduct **3.3id** in 65% yield and an e.r. of 85:15 (entry 7).

Table 3.6: Enantioselective conjugate addition optimisation of **3.1i**

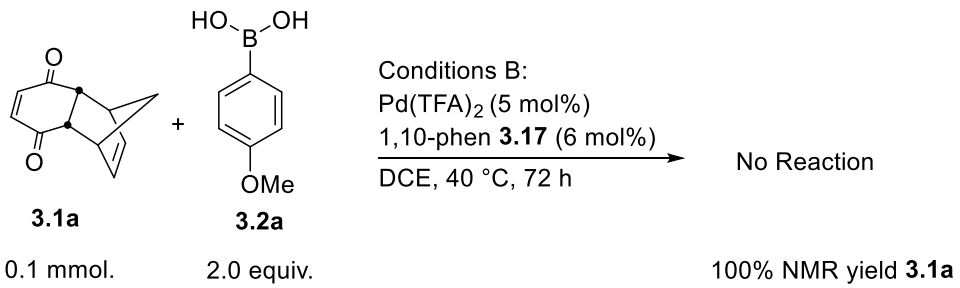


Entry	Conditions	Ligand	NMR Yield (%)[a] 3.3id:3.9id	e.r.[b] 3.3id	e.r.[b] 3.9id
1	A	^{t}BuPyOx **3.5**	9:91	84:16	59:41
2[d]	A	^{t}BuPyOx **3.5**	5:19	n.d.[c]	n.d.[c]
3	A	4-CF$_3$^{t}BuPyOx **3.7**	11:87	86:14	68:32
4	A	5-CF$_3$^{t}BuPyOx **3.6**	3:34	77:23	64:36
5	B	4-CF$_3$^{t}BuPyOx **3.7**	68(65)[e]:-	85:15	-
6	B	5-CF$_3$^{t}BuPyOx **3.6**	48:-	80:20	-
7	B	^{t}BuPyOx **3.5**	21:-	67:33	-

[a] Yield determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as internal standard, [b] E.r. determined by chiral stationary phase HPLC. [c] Not determined. [d] Reaction carried out under air instead of oxygen. [e] Isolated yield of **3.3id**.

3.4.3.4 Coupling of Diels-Alder adduct 3.1a with conditions B

Conditions B had been successfully applied to Diels-Alder adducts **3.1g**, **3.1h**, and **3.1i** which behaved differently under conditions A. Therefore, it was appropriate to attempt conditions B with Diels-Alder adduct **3.1a**, which had so far failed to achieve any coupling (Scheme 3.14). Unfortunately, we were not able to get any racemic coupling under conditions B, substituting (*S*)-PyOx ligands for 1,10-phen **3.17**. Substrate **3.1a** was therefore unreactive under both conditions A as well as B.

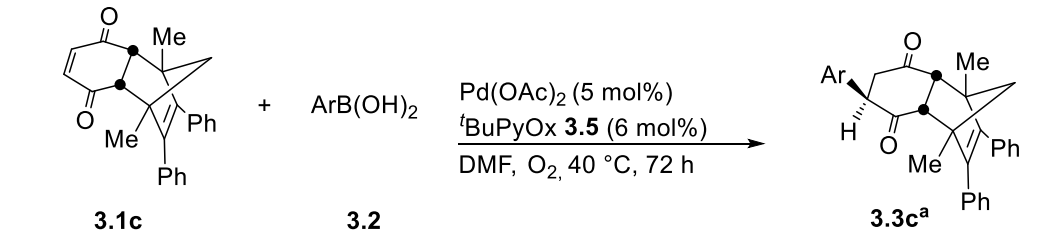


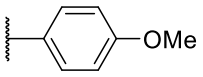
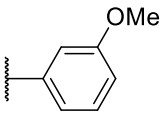
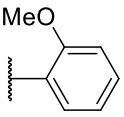
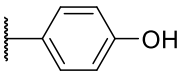
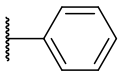
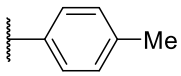
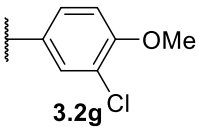
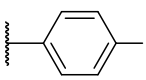
Scheme 3.14: Attempted coupling of **3.1a** under racemic conditions B

3.5 Aryl Boronic Acid Scope

Next, our attentions were turned to the aryl boronic acid scope of our conjugate addition desymmetrisation reaction (Table 3.7). It was decided that the aryl boronic acid **3.2** scope should be carried out with dimethyl-diphenyl Diels-Alder adduct **3.1c** as it was desymmetrised to excellent e.r. during the Diels-Alder adduct **3.1** scope studies. Furthermore, the symmetric cyclopentadiene **3.10c** was straightforward to prepare in bulk, as discussed in Section 3.4.1.

Table 3.7: Aryl boronic acid **3.2** screen



3.1c	**3.2**			
0.1 mmol	2.4 equiv.			
				
3.2a	**3.2b**	**3.2c**	**3.2d**	**3.2e**
70%, 97:3 e.r.	58%, 97:3 e.r.	46%,[b] 92:8 e.r.	65%, 98:2 e.r.	83%,[b,c] 97:3 e.r.
				
3.2f	**3.2g**	**3.2h**	**3.2i**	**3.2j**
81%,[b,c] 97:3 e.r.	51%,[b] 97:3 e.r.	67%[b,c] (80%),[d] 94:6 e.r.	42%[b,e] (60%),[d] 98:2 e.r.	13%,[f,g] 95:5 e.r.

[a] Isolated yield, >20:1 d.r., determined by ^{1}H NMR analysis, enantiomeric ratio determined by CSP-HPLC. [b] Carried out with $Pd(OAc)_2$ (10 mol%), *t*BuPyOx **3.5** (11 mol%). [c] Increased ligand and catalyst loading to promote full conversion to product due to co-elution with starting material during column chromatography. [d] NMR yield determined by ^{1}H NMR analysis by with internal standard 1,3,5-trimethoxybenzene. [e] Reacted for 92 h. [f] Portion-wise addition of catalyst and ligand, 5/6 mol% at the start, then a further 5/6 mol% after 24 h. [g] Reacted at 50 °C

Meta- **3.2b** and *para*-methoxy **3.2a** aryl boronic acids both react with Diels-Alder adduct **3.1c** to give excellent 97:3 e.r. and good yields (**3.2a**, 70% and **3.2b**, 58%). *ortho*-Methoxyphenyl boronic acid **3.2c** required a higher catalyst and ligand loading (10/11 mol%) in order to yield **3.3cc** in 46% and 92:8 e.r., showing a clear steric trend. *p*-Hydroxyphenyl boronic acid **3.2d** also reacted well (65%, 98:2 e.r.). Phenyl **3.2e** (83%, 97:3 e.r.) and methyl substituents **3.2f** (81%, 97:3 e.r.) are also tolerated in the reaction. It should be noted that these boronic acids did not require a higher catalyst and ligand loading to promote the reaction, but rather to promote *full* conversion to product to

improve purification. The starting material and conjugate addition product co-eluted on silica gel column chromatography so any remaining starting material **3.1c** could not be removed if the reaction did not go to completion. Pleasingly, electron-withdrawing halogen substituted boronic acids are tolerated well to furnish the desired conjugate addition products **3.3cg** (51%, 97:3 e.r.) and **3.3ch** (67%, 94:6 e.r.) in good yield and very good enantioselectivities. *p*-Amidophenyl boronic acid **3.2i** also reacted with *meso*-polycyclic cyclohexanedione **3.1c** to give **3.3ci** in moderate isolated yield (42%) but excellent e.r. of 98:2. Unfortunately, electron-withdrawing *para*-ethyl ester functionalised boronic acid **3.2j** only furnished 13% yield of **3.3cj** but a pleasing 95:5 e.r., even with portionwise addition. Phenol formation was an issue with this boronic acid, however, a saturated potassium carbonate wash was sufficient to remove this by-product.

It should be noted that *p*-fluorophenyl **3.2h** and *p*-amidophenyl **3.2i** boronic acids both reacted with better yields than the isolated yield suggests. *p*-Fluorophenyl product **3.3ch** also co-eluted with starting material **3.1c**, however, using 10/11 mol% catalyst and ligand loading did not promote full conversion to product, instead yielding **3.3ch** in 80% NMR yield, with 10% starting material remaining. The e.r. was recorded from the columned starting material/coupled product mixture but a recrystallisation was subsequently carried out to obtain an isolated yield of 67%. The same process was carried out for the *p*-amidophenyl conjugate addition product **3.3ci**, as it co-eluted with unidentifiable compounds. Compound **3.3ci** was formed in 60% NMR yield and the e.r. was recorded on the mixture partially purified by column chromatography, and subsequently recrystallisation gave 42% isolated yield.

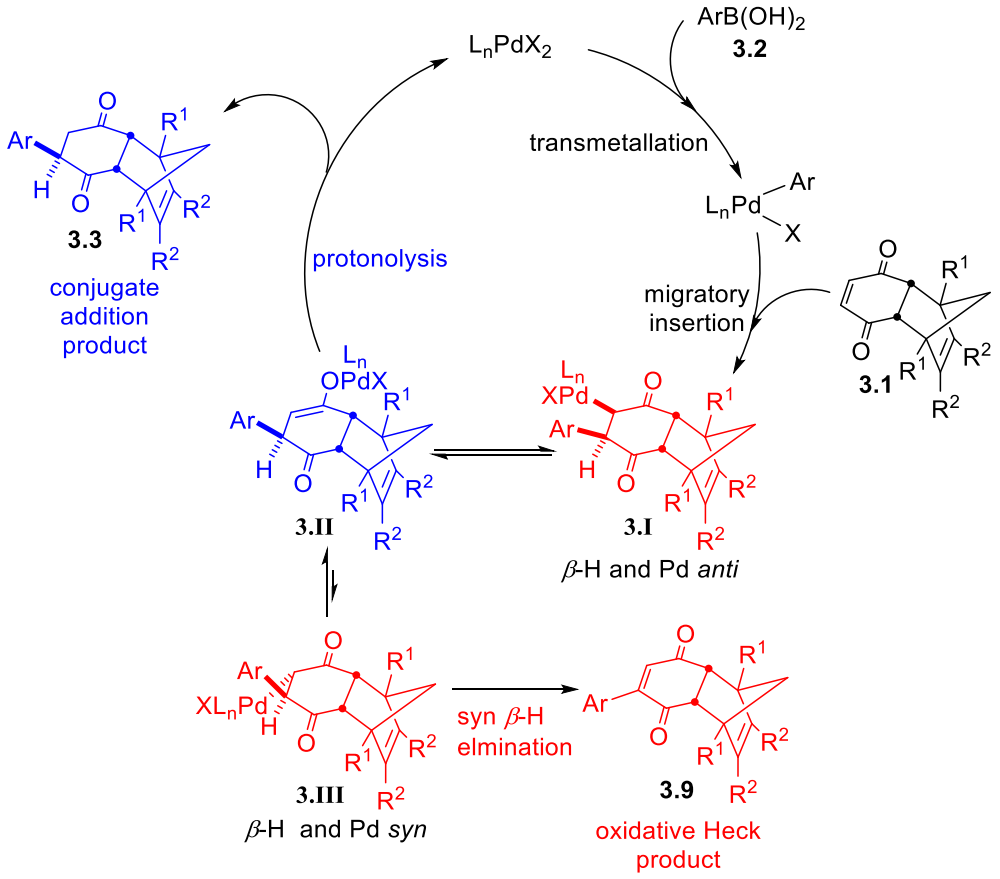
Increasing the reaction temperature was not a successful method for improving the yields during the boronic acid **3.2** scope studies. In the enantioselective optimisation

(Section 3.3.2), it was seen that increasing the reaction temperature had an adverse effect on the e.r. of the product. Whenever we attempted to improve the yield of the conjugate addition reaction during the boronic acid **3.2** scope studies, increased reaction temperatures did not improve yields. Instead, a crude complex mixture of products was observed by ^{1}H NMR analysis. It is thought that there is a temperature limit to working with polycyclic Diels-Alder adducts **3.1** and the conjugate addition products **3.3**, as they start to undergo a retro-Diels-Alder reaction at higher temperature. This would result in a more complex crude reaction NMR and TLC, however, as several products are possible it was often very difficult to confirm that this had happened.

3.5 Mechanism and Rationalisation of Product Selectivity

3.5.1 Mechanism and Rationalisation for Observed Product Selectivity

As discussed in Chapter 1, Section 1.2.6 and 1.4, the proposed mechanisms for Pd(II)-catalysed conjugate addition and oxidative Heck reactions of an aryl boronic acid with a cyclic enone are very similar (Scheme 3.15).[27] They only deviate at the final step on release of the product from the cycle: *syn* β-hydride elimination to yield the Heck-type product **3.9** or protonolysis to furnish the conjugate addition product **3.3**.



Scheme 3.15: Proposed conjugate addition and oxidative Heck catalytic cycles

In our investigations to desymmetrise Diels-Alder adducts **3.1**, we have been using what are typically considered to be oxidative Heck reaction conditions (conditions A). Therefore, when we initiated our studies, we were surprised to access the conjugate addition product **3.3** selectively (except in documented cases, see Section 3.4.3.3 and Appendix I). The Lee group has previously carried out investigations into controlling the formation of the conjugate addition product *versus* the oxidative Heck product with cyclohexenone.[27] A key finding was that the solvent was very important in determining the selectivity of which product was synthesised. In order to selectively yield the conjugate addition product, the group found chlorinated solvents such as DCE to be vital. On the other hand, polar aprotic solvents such as DMSO were thought to be important for the formation of the oxidative Heck product. In our later works, with the

aim of carrying out enantioselective oxidative Heck desymmetrisation reactions, we found polar aprotic solvents DMF or DMA to be imperative to accessing the oxidative Heck product.[1, 2]

The group hypothesised that polar aprotic solvents influenced the catalytic cycle (Scheme 3.15). After migratory insertion to form intermediate **3.I**, the Pd catalyst and the *β*-H required for elimination are in an *anti*-relationship. An epimerisation through Pd-enolate **3.II** is required to access intermediate **3.III** where *syn β*-hydride elimination can now occur to furnish oxidative Heck product **3.9**. The group postulated that the use of polar aprotic solvents facilitated this epimerisation process from **3.I→3.III**, thus making oxidative Heck chemistry possible. Therefore, it was surprising to yield conjugate addition product **3.3** with **3.1** utilising conditions A, which are typical oxidative Heck reaction conditions.

Although unproven, we believe that the root of this unexpected reactivity lies with two factors: the shape of Diels-Alder adduct **3.1**, and the epimerisation from intermediate **3.I→3.III** (Scheme 3.15). X-ray crystal structures of Diels-Alder adducts **3.1b** and **3.1i** (Figure 3.5)**,** make it clear that these molecules have an open top face (*exo*-face) and a very sterically restrictive bottom face (*endo*-face). Furthermore, the Diels-Alder adducts also appear to be quite rigid, with limited conformational flexibility. After migratory insertion, the aryl group is delivered to the *exo*-face, with the Pd catalyst residing on the carbon adjacent, also on the *exo*-face (Scheme 3.15, intermediate **3.I**). As discussed above, to obtain the oxidative Heck product, an epimerisation process from **3.I** through Pd-enolate **3.II** to intermediate **3.III** must occur to allow for *syn β*-hydride elimination. In the case of our Diels-Alder adducts **3.1**, we hypothesise that this epimerisation is unfavourable. For intermediate **3.III** to form, this would place the Pd catalyst on the sterically crowded *endo*-face of the Diels-Alder adduct. If this epimerisation process is

too high in energy to occur, then the oxidative Heck product **3.9** cannot be formed as *syn* β-hydride elimination is only possible through intermediate **3.III**. We therefore hypothesise that protonolysis is much lower in energy and hence the selectivity for the conjugate addition product **3.3** for these Diels-Alder adducts **3.1**.

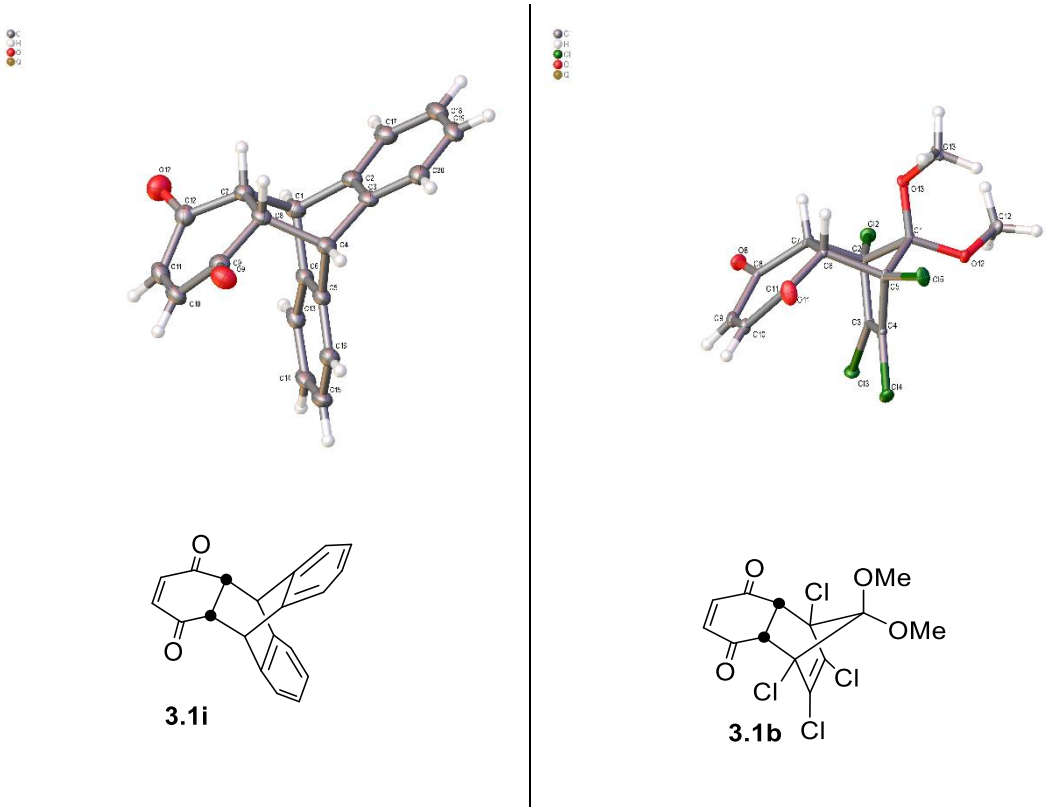
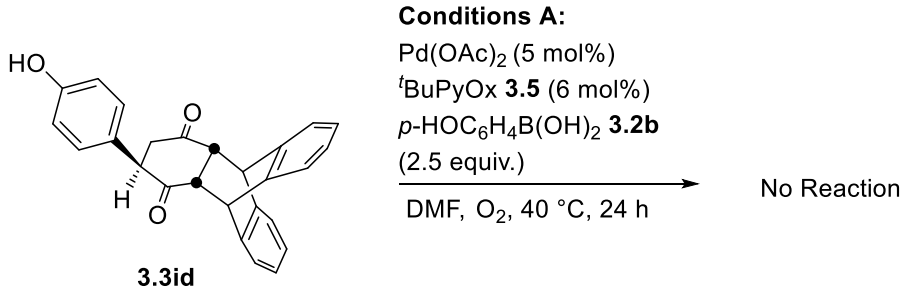


Figure 3.5: Single crystal X-ray structures of Diels Alder adduct **3.1i** and **3.1b**

3.5.2 Anthracene Diels-Alder Adduct 3.1i

Within the Diels-Alder adduct **3.1** scope, it was found that one substrate behaved slightly differently to the rest of the substrates. Diels-Alder adduct **3.1i**, under conditions A, gave a mixture of conjugate addition **3.3id** and oxidative Heck products **3.9id**. This is the only substrate where the tri-cyclic system is constructed from three 6-membered rings as opposed to one 6-membered ring and two 5-membered rings. This may lead to a slightly larger degree of conformational flexibility than is possible with the other Diels-Alder adducts in this study. However, this hypothesis is unproven.

In order to ascertain whether the oxidative Heck product **3.9** is the result of a true oxidative Heck reaction, formed through *syn* β-hydride elimination, or conjugate addition followed by dehydrogenation, a control reaction was carried out. Pure conjugate addition coupled product **3.3id**, furnished through the employment of conditions B, was re-subjected to conditions A, under which we originally observed oxidative Heck product **3.9id** (Scheme 3.16). After 24 h, no trace of oxidative Heck product **3.9id** was observed in the crude reaction mixture by ^{1}H NMR spectroscopy. Therefore, the oxidative Heck product **3.9id** observed under conditions A is likely to be the result of a true oxidative Heck reaction rather than conjugate addition followed by dehydrogenation.



Scheme 3.16: Control reaction

3.6 Determination of Absolute Stereochemistry and Rationalisation of Absolute Stereochemistry

3.6.1 Determination of Absolute Stereochemistry

The absolute stereochemistry of the major enantiomer of the conjugate addition reaction was determined by single crystal x-ray analysis of **3.3ba.** C2, C7 and C10 were determined to be (*R*)-configuration and C5 and C6 were determined to be (*S*)-configuration (Figure 3.6). The absolute stereochemistry of all conjugate addition products **3.3** were assigned by analogy.

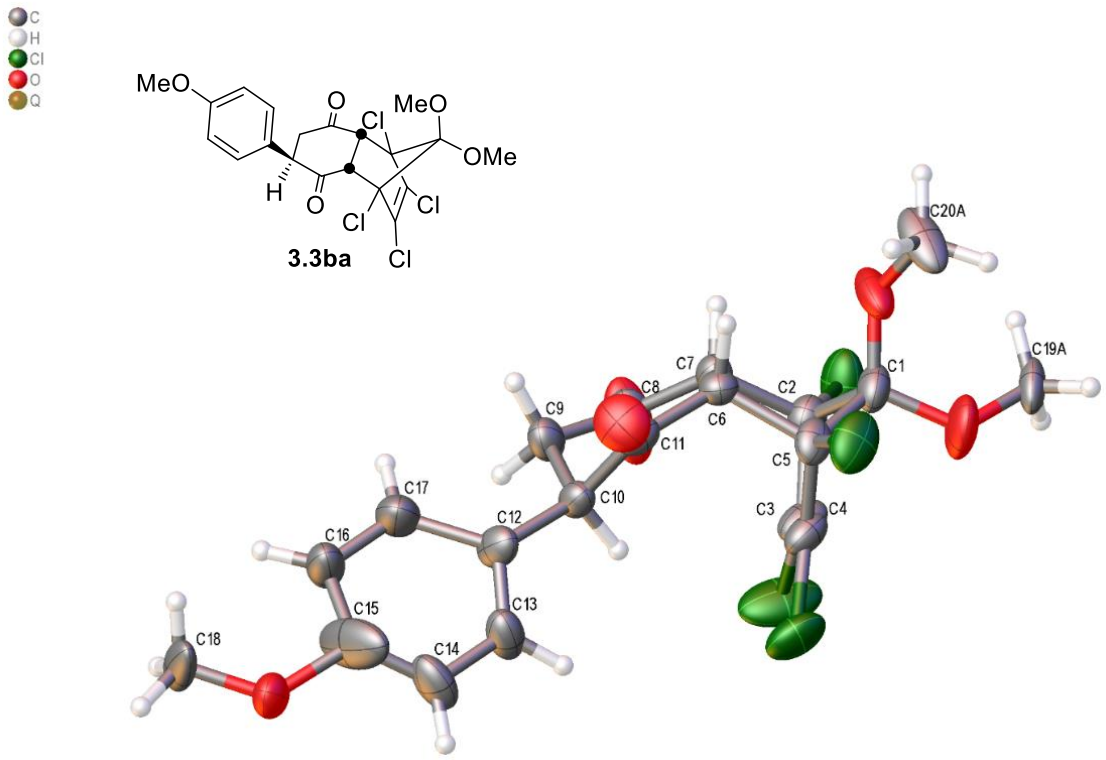


Figure 3.6: Crystal structure and Chemdraw structure of conjugate addition product **3.3ba**. Displacement ellipsoid plot of **3.3ba** with ellipsoids drawn at the 50% probability level and H atoms shown with spheres of arbitrary radii.

3.6.2 Rationalisation of Observed Absolute Stereochemistry

Computational modelling and mechanistic investigations were carried out by Stoltz *et al*. into enantioselective conjugate addition reactions with related cyclohexanone substrates using Pd(II)^{t}BuPyOx **3.5** as the catalyst.[26] During this study, they determined that migratory insertion is the enantio-determining step. They suggested a square-planar geometry transition state, where if analogous to our reaction, the transition state would consist of chiral ^{t}BuPyOx **3.5,** the aryl group from the boronic acid and the Diels-Alder adduct **3.1** (see Figure 3.7).

To rationalise the observed stereochemistry, two factors need to be considered in the proposed transition state: whether the aryl group of the boronic acid transmetallates *cis* or *trans* with respect to the chiral information of the oxazoline ligand, and the orientation of the Diels-Alder adduct enedione upon commencing migratory insertion. As such, there are four possible transition states to consider (Figure 3.7).

Furthermore, the Diels-Alder adduct enedione could bind on the *exo* or *endo*-face. This gives rise to a total of eight possible transition states to account for the observed enantioselectivity. However, as we have excellent diastereoselectivity in the conjugate addition coupled product **3.3**, we can immediately discount the Diels-Alder adduct binding *via* the *endo*-face as this would result in the opposite or a mixture of diastereomers being observed. Presumably this orientation of the Diels-Alder adduct **3.1** is too high in energy due to steric constraints.

Of the four proposed transition states in Figure 3.7, **TS-A** and **TS-D** lead to the correct (*R*)-geometry with respect to the stereocentre generated by aryl addition at the enedione. However, based on previous work by Stoltz *et. al.*[26], they suggest that it is more energetically favourable for the aryl group after transmetallation to be *trans* to the *tert*-

butyl group of the chiral ligand, due to reduced steric constraints. This rationale rules out **TS-D**. **TS-A** therefore, leads to the least amount of steric repulsion and is proposed to be the most energetically favourable transition state. However, further bespoke computational analysis would be necessary to confirm this theory.

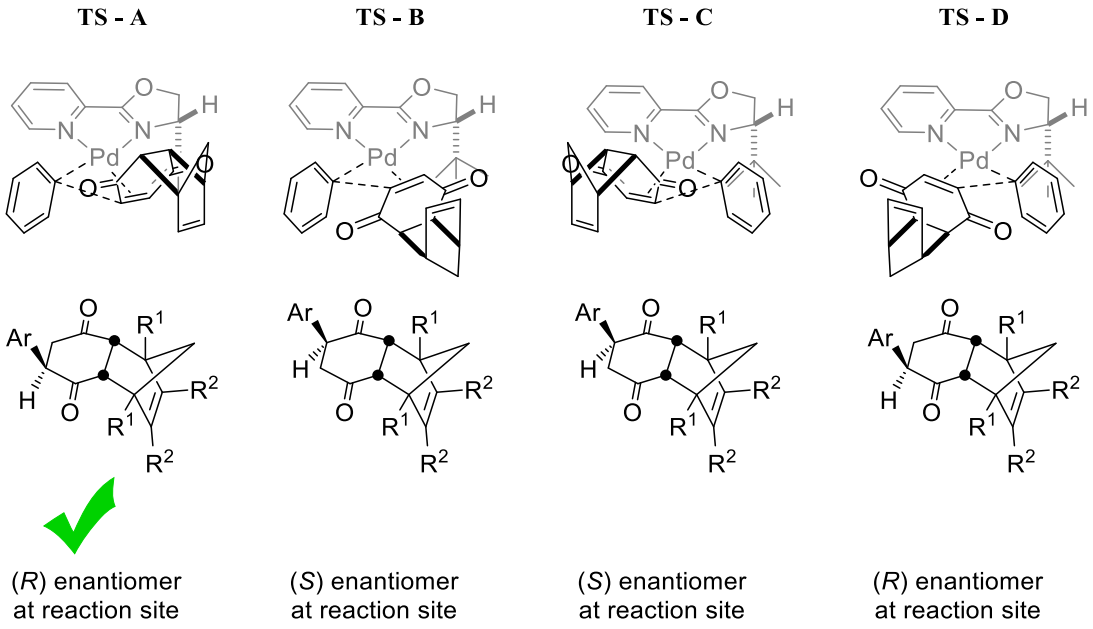
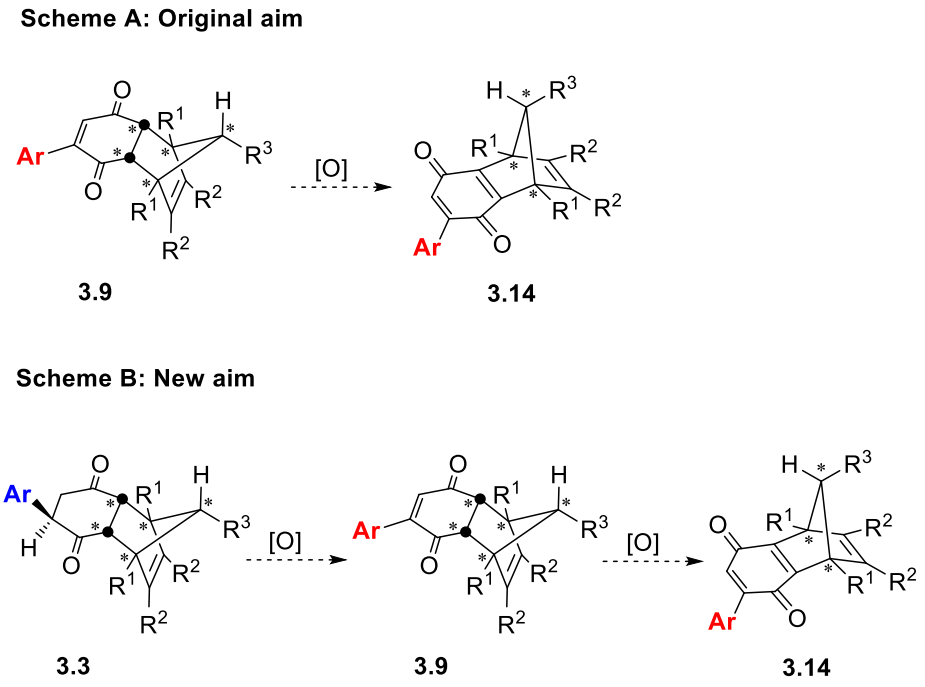


Figure 3.7: Possible enantio-determining transition states (substituents removed for clarity)

3.7 Attempted Synthesis of Heck-type and Benzoquinone Products

Our initial aim of this project was to develop an oxidative Heck desymmetrisation reaction of multiple stereocentres (Section 3.2, Scheme 3.5). We envisaged that this method could be a fast and efficient route to a class of chiral diene ligands. Furthermore, we aimed to carry out an oxidation of the coupled oxidative Heck product **3.9** to access a new type of chiral benzoquinone **3.14** ligand which could be tested for its catalytic ability (Scheme 3.17A).



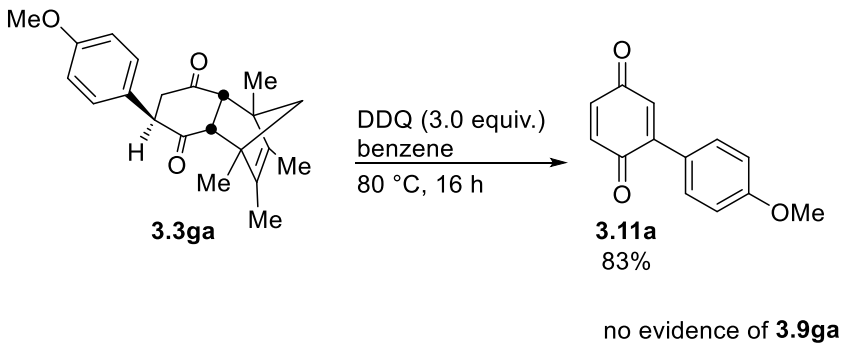
Scheme 3.17: Aim: to oxidise **3.3** to access chiral dienes and benzoquinones

As discussed throughout Chapter 3, the Heck-type product **3.9** unfortunately could not be synthesised directly through Pd(II) catalysis, and instead the conjugate addition product **3.3** was furnished exclusively. The original aim (Scheme 3.17A) was therefore revised to dehydrogenation of the enantioenriched conjugate addition product **3.3** to access the chiral Heck-type product **3.9** or the benzoquinone **3.14** (Scheme 3.17B).

Several oxidants and methods including 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (Scheme 3.18),[32, 33] chloranil,[33] 2-iodoxybenzoic acid (IBX, Table 3.8)[34, 35] and Pd(II)-catalysed aerobic oxidations were attempted.[2, 22] Unfortunately, all efforts to access the Heck-type product **3.9** or the chiral benzoquinone **3.14** through oxidation of the conjugate addition product **3.3** were unsuccessful.

Generally, the oxidation protocols which required high temperature often resulted in retro-Diels-Alder reactions (e.g. DDQ, Scheme 3.18). Furthermore, it is now thought that Diels-Alder adducts **3.1** or conjugate addition products **3.3** are unstable under acidic

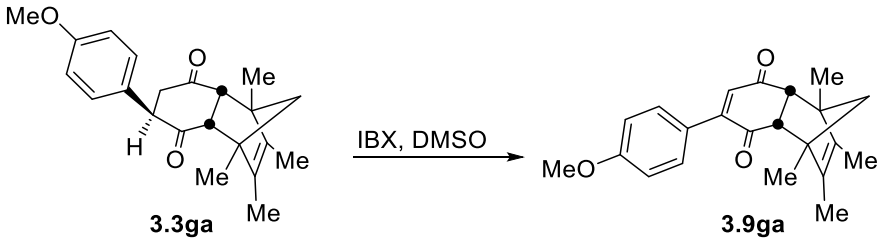
conditions (e.g. Stahl's Pd(II)-catalysed aerobic oxidation). Only complex mixtures were observed when acid conditions were employed, with no evidence of starting material **3.3** remaining.



Scheme 3.18: Attempted dehydrogenation of **3.3ga** with DDQ

The employment of IBX as oxidant provided the most promising results (Table 3.8). Oxidation of **3.3ga** to **3.9ga** was promoted using IBX; regrettably, the yield could not be improved beyond 34% and the oxidation could not be pushed to completion (entry 4). Furthermore, **3.3ga** and **3.9ga** could not be easily separated by column chromatography. A milder protocol utilising *N*-pyridine oxide with IBX was also attempted, as *N*-pyridine oxide with IBX was shown in the literature to be active to facilitate dehydrogenation at lower temperatures (entries 6 and 7).[35] However, these conditions were not successful in promoting any dehydrogenation of **3.3ga**.

Table 3.8: Attempted oxidation of **3.3ga** with IBX



3.3ga **3.9ga**

Entry	Temp (°C)	IBX (equiv.)	Time (h)	Yield (%)[a]	
				3.3ga	**3.9ga**
1	65	1.5	21	32	48
2	65	1.5	21	33	40
3	65	3.0	24	22	37
4	65	2.0	48	34	23
5[b]	65	3.0	48	33	30
6[c]	40	1.5	48	94	-
7[d]	40	3.0	48	94	-

[a] Yield determined by ^{1}H NMR spectroscopy by comparison with internal standard 1,3,5-trimethoxybenzene. [b] Portionwise addition of IBX, 1.5 equiv. at the start followed by another 1.5 equiv. added after 24 h. [c] Reaction with *N*-pyridine oxide (1.5 equiv.) [d] Reaction with *N*-pyridine oxide (3.0 equiv.)

Unfortunately, due to time constraints this work was not taken any further. However, there is still potential for future work in this area to achieve the aim of accessing enantioenriched dienes **3.9** and benzoquinones **3.14** (Scheme 2.17B).

It should be noted that Diels-Alder adduct **3.1i** behaved quite differently in the Pd(II)-catalysed reaction (producing the oxidative Heck product **3.9id** as well as conjugate addition product **3.3id**, see Section 3.4.3), and that these products also behaved differently in the oxidation reactions. Further information of these studies is detailed in Appendix I.

3.8 Conclusions

In conclusion, although we did not achieve our original aim of developing a Pd(II)-catalysed oxidative Heck desymmetrisation reaction on systems with multiple pro-stereogenic centres; we have developed an equally interesting Pd(II)-catalysed conjugate addition on Diels-Alder adducts **3.1**. Up to five contiguous stereocentres were desymmetrised, including quaternary centres, with the creation of a further stereocentre in one efficient reaction. This was achieved in good yield and in excellent e.r. and d.r. (up to 98:2 e.r. and >20:1 d.r.). The absolute stereochemistry was determined by single crystal X-ray analysis. Anthracene Diels-Alder adduct **3.1i** gave interesting results; **3.1i** was the only substrate where the desired oxidative Heck product **3.9id** was accessed.

Although attempts at the dehydrogenation of the conjugate addition products **3.3** to form potential chiral ligands **3.9** or **3.14** were met with limited success due to time constraints, future work could focus on investigating alternative oxidation reagents such as SeO_2.

3.9 Experimental Section

3.9.1 General Experimental Considerations

^{1}H NMR spectra were recorded on Bruker AV 300 and AV 400 spectrometers at 300 and 400 MHz respectively and referenced to residual solvent. ^{13}C NMR spectra were recorded using the same spectrometers at 75 and 100 MHz respectively. Chemical shifts (δ in ppm) were referenced to residual solvent peaks ($CDCl_3$ at δ_H 7.26, δ_C at 77.16 ppm.)

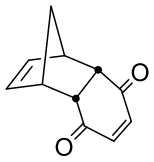
J values are given in Hz and s, d, dd, t, q, qn and m abbreviations correspond to singlet, doublet, doublet of doublet, triplet, quartet, quintet and multiplet. Mass spectra were obtained at the EPSRC UK National Mass Spectrometry Facility at Swansea University. Infrared spectra were obtained on Perkin-Elmer Spectrum 100 FT-IR Universal ATR Sampling Accessory, deposited neat or as a chloroform solution to a diamond/ZnSe plate. Flash column chromatography was carried out using Matrix silica gel 60 from Fluorochem and TLC was performed using Merck silica gel 60 F254 pre-coated sheets and visualised by UV (254 nm) or stained by the use of aqueous acidic $KMnO_4$ or aqueous acidic ceric ammonium molybdate as appropriate. Enantiomer separation was achieved by chiral stationary phase HPLC (CSP-HPLC) with an Agilent Technologies 1120 Compact LC with either CHIRALPAK IA, IB or IC column as appropriate. Optical rotation was measured on a Bellingham and Stanley ADP410 polarimeter.

Where petroleum ether is stated it refers to petroleum ether (40–60 °C). Anhydrous DMF was obtained from a solvent purification system. All aryl boronic acids were purchased from Sigma-Aldrich, Fluorochem or Acros. In most circumstances, the aryl boronic acid could be used directly from the bottle. In specific cases where the corresponding boroxine or recrystallised boronic acids performed better, this is

documented in the relevant reaction. The coupling reactions were carried out in dried glassware, using either anhydrous DMF from a solvent purification system and $Pd(OAc)_2$ from Johnson Matthey, or using DCE from Acros stored over 4 Å MS and $Pd(TFA)_2$ synthesised according to literature procedure with minor modifications.[36]

3.9.2 Diels-Alder Adduct 3.1 Synthesis

1,4,4a,8a-Tetrahydro-1,4-methanonaphthalene-5,8-dione 3.1a[37]

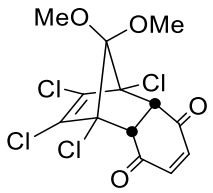


3.1a

To an oven dried flask, back-filled with argon, *p*-benzoquinone **3.11** (1.082 g, 10.00 mmol, 1.00 equiv.) was dissolved in DCM (5 mL) and stirred at 0 °C. Cyclopentadiene **3.10a** (0.85 mL, 10.40 mmol, 1.04 equiv.) was added drop-wise over 1.5 h and the reaction was left to stir at 0 °C for 1 h, and then warmed to room temperature and stirred for a further 30 minutes. The reaction was concentrated under reduced pressure. The crude mixture was recrystallised from hot hexane, left to cool on ice and filtered to yield **3.1a** (1.54g, 8.81 mmol, 88% yield) as pale-yellow crystals.

Mp: 53-54 °C (hexane) (literature mp: 50-52 °C);[38] R_f: 0.28 in 5:1 petroleum ether/EtOAc; ν_{max}/ cm^{-1}: 3028, 2979, 2925, 1755, 1715, 1453, 1438, 1410, 1372, 1326, 1199, 1078, 995, 789, 758, 705; ^1H NMR (400 MHz, $CDCl_3$) δ 6.57 (s, 2H, =CH), 6.07 (app. t, *J* = 1.8 Hz, 2H, =CH), 3.57 – 3.53 (m, 2H, CH), 3.22 (dd, *J* = 2.4, 1.5 Hz, 2H CH), 1.54 (dt, *J* = 8.8, 1.8 Hz, 1H, C<u>H</u>H), 1.43 (dm, *J* = 8.8 Hz, 1H, CH<u>H</u>); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.6 (C), 142.2 (CH), 135.4 (CH), 48.9 (CH), 48.9 (CH_2), 48.5 (CH).

1,2,3,4-Tetrachloro-9,9-dimethoxy-1,4,4a,8a-tetrahydro-1,4-methanonaphthalene-5,8-dione 3.1b[13]

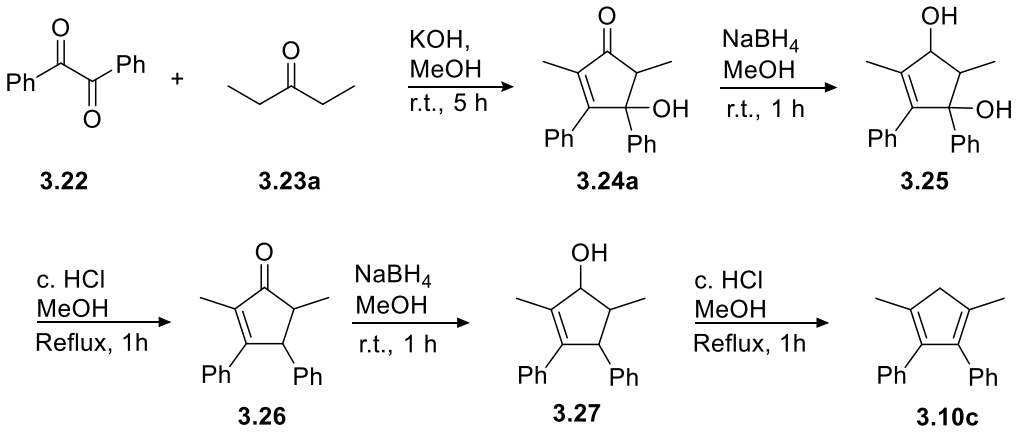


3.1b

To oven dried reflux apparatus, back-filled with argon, 1,2,3,4-tetrachloro-5,5-dimethoxycyclopentadiene **3.10b** (498.7 mg, 1.89 mmol, 1.00 equiv.) was stirred in toluene for 5 minutes before *p*-benzoquinone **3.11** (209.1 mg, 1.93 mmol, 1.02 equiv.) was added and the reaction was stirred at reflux for 18 h. The reaction was cooled, and solvent was removed under reduced pressure. The resulting residue was purified by silica gel column chromatography (12:1 → 5:1 petroleum ether: EtOAc) to yield **3.1b** (610.0 mg, 1.64 mmol, 87%) as a crystalline yellow powder.

Mp: 160–163 °C (EtOAc/petroleum ether) (literature mp: 156–158 °C)[13]; R_f: 0.2 in 12:1 petroleum ether:EtOAc; ν_{max}/ cm^{-1}: 3025, 2932, 1674, 1014, 736 ; ^1H NMR (300 MHz, $CDCl_3$) δ 6.72 (s, 2H, =CH), 3.66 (s, 3H, OCH_3), 3.63 (s, 2H, CH), 3.60 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.8 (C), 142.2 (CH), 129.5 (C), 111.2 (C), 77.9 (C), 54.9 (CH), 53.4 (CH_3), 52.4 (CH_3).

(3,5-Dimethylcyclopenta-2,5-diene-1,2-diyl)dibenzene 3.10c[29]



3.22 **3.23a** **3.24a** **3.25**

3.26 **3.27** **3.10c**

Benzil **3.22** (4.21 g, 20.0 mmol, 1.0 equiv.) and pentan-3-one **3.23a** (1.73 g, 20.0 mmol, 1.0 equiv.) were dissolved in ethanol absolute (10 mL), potassium hydroxide pellets (218.6 mg, 3.0 mmol, 0.15 equiv.) were added and the reaction was stirred at room temperature for 16 h. The reaction was then acidified with HCl (1M) and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and solvent was removed under reduced pressure to yield **3.24a** (5.15 g, 18.5 mmol, 92%) as a pale-yellow powder and as mixture of diastereomers. The crude product was taken forward without further purification.

3.24a (3.80 g, 13.7 mmol, 1.0 equiv.) was dissolved in methanol (40 mL), $NaBH_4$ (574.3 mg, 15.0 mmol, 1.1 equiv.) was added in portions and the reaction was stirred at room temperature for 1 h. The reaction was quenched with water (2.5 mL) and extracted with DCM (3 × 20 mL), the combined organic layers were washed with brine and dried over $MgSO_4$. Solvent was removed under reduced pressure to yield **3.25** (3.50 g, 12.5 mmol, 88%) as an off-white powder and as a mixture of diastereomers. The crude product was taken forward without further purification.

3.25 (5.40 g, 19.2 mmol, 1.0 equiv.) was dissolved in methanol (40 mL) and conc. HCl (4 mL) was added. The mixture was stirred at reflux for 1.5 h. Upon completion, the

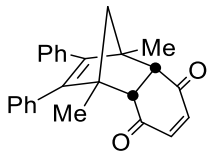
reaction mixture was neutralised with NaOH (1M) and extracted with DCM (3 × 20 mL) and the combined organic layers were washed with brine and dried over $MgSO_4$. Solvent was removed under reduced pressure. The resulting crude product was purified by recrystallisation with DCM/Petrol to yield **3.26** (5.02 g, 19.1 mmol, 99%) as white crystalline powder and as a mixture of diastereomers.

3.26 (4.00 g, 15.2 mmol, 1.0 equiv.) was dissolved in methanol (40 mL), $NaBH_4$ (638.0 mg, 16.9 mmol, 1.1 equiv.) was added in portions and the reaction was stirred at room temperature for 1 h. The reaction was quenched with water (2.5 mL) and extracted with DCM (3 × 20 mL), the combined organic layers were washed with brine and dried over $MgSO_4$ and solvent was removed under reduced pressure. The resulting crude was recrystallised with hot hexanes to yield **3.27** (3.90 g, 14.7 mmol, 97%) as white crystalline prisms and as a mixture of diastereomers.

3.27 (4.00 g, 15.1 mmol, 1.0 equiv.) was dissolved in methanol (50 mL) and conc. HCl (5 mL) was added. The mixture was stirred at reflux for 1.5 h. The reaction mixture was then neutralised with NaOH (1M) and transferred to a separating funnel. The organic layer was extracted with DCM (3 × 20 mL) and the combined organic layers were washed with brine and dried over $MgSO_4$. Solvent was removed under reduced pressure. The resulting crude product was purified by recrystallisation with hot methanol to yield **3.10c** (3.50 g, 14.2 mmol, 94%) as yellow crystalline needles.

Mp: 87 °C (methanol) (literature mp: 89-90 °C);[29] R_f: 0.9 in petroleum ether; ν_{max}/ cm^{-1}: 2905, 2850, 1603, 1494, 755, 703; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 – 7.13 (m, 6H, Ar-H), 7.00 – 6.92 (m, 4H, Ar-H), 3.14 (s, 2H, CH_2), 2.06 (s, 6H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.6 (C), 136.8 (C), 136.5 (C), 129.7 (CH), 127.7 (CH), 126.1 (CH), 50.1 (CH_2), 14.6 (CH_3).

1,4-Dimethyl-2,3-diphenyl-1,4,4a,8a-tetrahydro-1,4-methanonaphthalene-5,8-dione 3.1c[13]

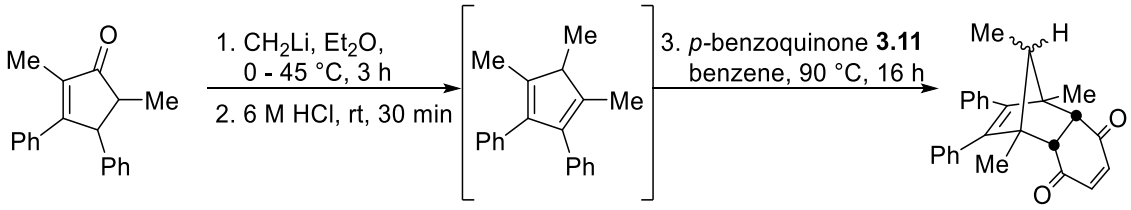


3.1c

p-Benzoquinone **3.11** (200 mg, 1.85 mmol, 1 equiv.) was dissolved in benzene (5 mL), **3.10c** was then added (547 mg, 2.22 mmol, 1.2 equiv.) and the reaction was stirred at reflux for 16 h. The reaction was then cooled, and solvent was removed under reduced pressure. The resulting crude was purified by silica gel column chromatography (10:1 → 5:1 petroleum ether/EtOAc) to yield **3.1c** (620.0 g, 1.75 mmol, 95%) as a yellow powder.

Mp: 158 °C (methanol) (literature mp: 147-149 °C)[13]; R_f: 0.2 in 10:1 petroleum ether:EtOAc; ν_{max}/ cm^{-1}: 2930, 2858, 1757, 1659, 1038, 752, 700; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08 – 7.01 (m, 6H, Ar-H), 6.78 – 6.70 (m, 4H, Ar-H), 6.55 (s, 2H, HC=CH), 3.16 (s, 2H, HC-CH), 1.80 (d, *J* = 8.6 Hz, 1H, C<u>H</u>H), 1.59 (d, *J* = 8.6 Hz, 1H, CH<u>H</u>), 1.49 (s, 6H, 2 × CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.2 (C), 145.9 (C), 142.4 (CH), 134.9 (C), 129.6 (CH), 128.1 (CH), 127.0 (CH), 65.1 (CH_2), 59.5 (C), 57.3 (CH), 18.4 (CH_3).

1,4,9-Trimethyl-2,3-diphenyl-1,4,4a,8a-tetrahydro-1,4-methanonaphthalene-5,8-dione 3.1d[13]



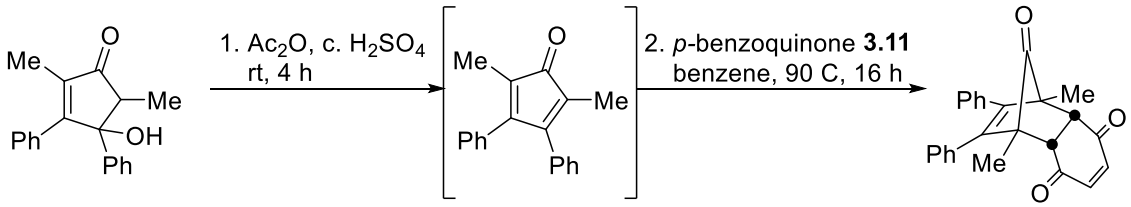
3.26 **3.10d** **3.1d**

To a two-necked flask, oven dried and back-filled with N_2, **3.26** (500.0 mg, 1.90 mmol, 1.0 equiv.) was dissolved in dry Et_2O (5 mL) and cooled to 0 °C. CH_3Li in Et_2O (1.56 mol L^{-1}, 1.65 mL, 2.57 mmol, 1.4 equiv.) was added drop-wise before the reaction mixture was warmed to room temperature and then stirred at reflux for 3 h. The reaction was then cooled to room temperature. HCl (6 M, 3 mL) was added dropwise and the reaction was stirred for a further 30 min. The reaction was quenched with saturated sodium bicarbonate solution (5 mL) and extracted with DCM (3 × 10 mL), the combined organic layers were dried over Na_2SO_4 and solvent was removed under reduced pressure. The resulting crude of **3.10d** was used in the next step without further purification due to being prone to isomerisation.[29]

The crude of **3.10d** was transferred to a round bottom flask containing *p*-benzoquinone **3.11** (173 mg, 1.60 mmol, 0.84 equiv.) and benzene (4mL) and the reaction was stirred at reflux for 16 h. Solvent was then removed under reduced pressure. The resulting crude was purified by silica gel column chromatography (20:1→10:1 petroleum ether/EtOAc) to yield **3.1d** (122.2 mg, 0.33 mmol, 17%) as a yellow powder and 7:1 mixture of diastereomers. This is consistent with the literature reported procedure and spectra.[13]

Mp: 129-132 °C (petroleum ether:EtOAc) (literature mp: 123-125 °C)[13]; R_f: 0.2 in 10:1 petroleum ether:EtOAc; ν_{max}/ cm^{-1}: 2970, 2927, 1659, 1602, 777, 757, 699; NMR data for the major diastereomer: ^1H NMR (300 MHz, $CDCl_3$) δ 7.15 – 7.06 (m, 6H, Ar-H), 6.83 – 6.73 (m, 4H, Ar-H), 6.65 (s, 2H, HC=), 3.16 (s, 2H, CH), 1.81 (q, *J* = 6.3 Hz, 1H, C<u>H</u>CH_3), 1.42 (s, 6H, CH_3), 0.97 (d, *J* = 6.3 Hz, 3H, CHC<u>H</u>$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.1 (C), 142.6 (C), 142.5 (CH), 135.4 (C) , 129.3 (CH), 128.1 (CH), 126.9 (CH), 66.1 (CH), 62.4 (C), 57.3 (CH), 16.1 (CH_3), 7.7 (CH_3).

1,4-Dimethyl-2,3-diphenyl-1,4,4a,8a-tetrahydro-1,4-methanonaphthalene-5,8,9-trione[39] 3.1e



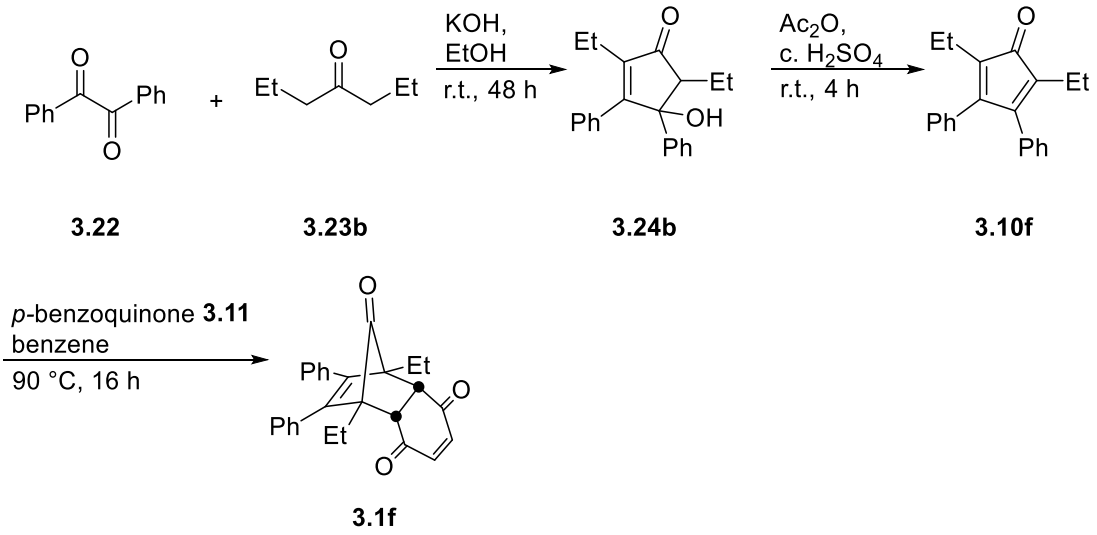
3.24a **3.10e** **3.1e**

A solution of **3.24a** (500.0 mg, 1.80 mmol, 1.0 equiv.) in acetic anhydride (2.0 mL, 21.1 mmol, 11.7 equiv.) was stirred at room temperature for 4 h. The bright red reaction mixture was quenched with H_2O (1 mL) and the precipitated product was collected by filtration and dried by reduced pressure to obtain the dimer of **3.10e** (315.8 mg) as pale yellow-solid which was used without further purification due to being prone to dimerisation.

Crude **3.10e** (315.8 mg, 1.2 mmol, 1.0 equiv.) was added to reflux apparatus containing *p*-benzoquinone **3.11** (195.8 mg, 1.80 mmol, 1.5 equiv.) and benzene (5 mL) and the resulting mixture was stirred at reflux for 16 h. Upon completion, solvent was removed under reduced pressure and the resulting crude was purified by silica gel column chromatography (20:1→3:1 petroleum ether/EtOAc) to yield **3.1e** (226.5 mg, 0.87 mmol, 51% yield) as a yellow powder.

Mp: 148-150 °C (Pet. Ether/EtOAc) (literature mp: 195-197 °C);[39] R_f: 0.2 in 5:1 petroleum ether:EtOAc; ν_{max}/cm^{-1}: 3026, 2928, 1775, 1760, 1668, 1611, 1575, 1445, 807; ^1H NMR (300 MHz, $CDCl_3$) δ 7.20 – 7.13 (m, 6H, Ar-H), 6.84 (s, 2H, HC=), 6.84 – 6.78 (m, 4H, Ar-H), 3.30 (s, 2H, CH), 1.54 (s, 6H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.8 (C), 195.8 (C), 143.9 (CH), 141.8 (C), 133.3 (C), 129.5 (CH), 128.4 (CH), 127.9 (CH), 59.0 (C), 52.0 (CH), 11.9 (CH_3).

1,4-Diethyl-2,3-diphenyl-1,4,4a,8a-tetrahydro-1,4-methanonaphthalene-5,8,9-trione 3.1f[13, 29, 30]



Benzil **3.22** (2.10 g, 10.0 mmol, 1.0 equiv.) and heptan-4-one **3.23b** (1.14 g, 10.0 mmol, 1.0 equiv.) were stirred in absolute ethanol (5 mL) at room temperature for 48 h. Upon completion, the reaction mixture was acidified with HCl (1 M) and was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and solvent with removed under reduced pressure to yield **3.24b** (2.21 g, 7.2 mmol, 72%) as a pale-yellow powder and as mixture of diastereomers. The crude product was taken forward to the next step without further purification.

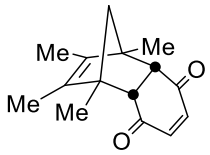
A solution of **3.24b** (551.5 mg, 1.8 mmol, 1.0 equiv.) in acetic anhydride (2.0 mL, 21.1 mmol, 11.7 equiv.) was stirred at room temperature for 4 h. The bright red reaction mixture was quenched with H_2O (1 mL) and the precipitated product was collected by

filtration and dried under reduced pressure to obtain **3.10f** (392.9 mg, 1.4 mmol, 76%) as bright orange solid which was used without further purification.

Crude **3.10f** (346.1 mg, 1.2 mmol, 1.0 equiv.) was added to reflux apparatus containing *p*-benzoquinone **3.11** (194.8 mg, 1.80 mmol, 1.5 equiv.) and benzene (5 mL) and the resulting mixture stirred at reflux for 16 h. The solvent was then removed under reduced pressure and the resulting crude was purified by silica gel column chromatography (10:1 petroleum ether/EtOAc) to yield **3.1f** (226.5 mg, 0.87 mmol, 51% yield) as a yellow crystalline solid.

Mp: 131-134 °C (Pet. Ether/EtOAc); R_f: 0.2 in 10:1 petroleum ether:EtOAc; νmax/cm^{-1}: 2676, 2922, 1765, 1671, 1607, 1464, 1447, 790 768, 704; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.17 – 7.11 (m, 6H, Ar-H), 6.85 (s, 2H, HC=), 6.83 – 6.76 (m, 4H, Ar-H), 3.61 (s, 2H, CH), 2.16 (dq, *J* = 14.6, 7.4 Hz, 2H, C<u>H</u>H), 1.93 (dq, *J* = 14.6, 7.4 Hz, 2H, CH<u>H</u>), 1.02 (t, *J* = 7.4 Hz, 6H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 199.3 (C), 196.3 (C), 143.8 (CH), 142.5 (C), 133.7 (C), 129.4 (CH), 128.3 (CH), 127.7 (CH), 62.4 (C), 47.2 (CH), 19.0 (CH_2), 9.3 (CH_3); HRMS (TOF MS ASAP +) *m/z calc.* for $C_{27}H_{25}O_3$: 397.1804 $[M+H]^+$; found: 397.1799.

1,2,3,4-Tetramethyl-1,4,4a,8a-tetrahydro-1,4-methanonaphthalene-5,8-dione 3.10g

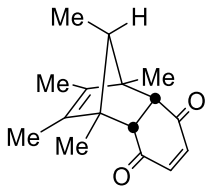


3.1g

1,2,3,4-Tetramethylcyclopentadiene **3.10g** (320 µL, 2.30 mmol, 1.0 equiv.) was added to a flask containing *p*-benzoquinone **3.11** (270.9 mg, 2.50 mmol, 1.0 equiv.) and benzene (1 mL). The reaction mixture was stirred at 30 °C for 4 hours. The solvent was then removed by reduced pressure and the crude mixture was recrystallised in hot hexanes to yield **3.1g** (526.1 mg, 2.28 mmol, 99%) as a yellow powder.

Mp: 129-132 °C (petroleum ether/EtOAc) (literature mp: 123-125 °C)[13]; R_f: 0.2 in 10:1 petroleum ether:EtOAc; ν_{max}/ cm^{-1}: 2960, 2928, 2864, 1753, 1743, 1661, 1442, 1380, 1115, 1073, 1034; ^1H NMR (400 MHz, $CDCl_3$) δ 6.47 (s, 2H, =CH), 2.93 (s, 2H, CH), 1.42 (s, 6H, CH_3), 1.40 (s, 6H, CH_3), 1.31 (d, *J* = 8.3 Hz, 1H, C<u>H</u>H), 1.26 (d, *J* = 8.3 Hz, 1H, CH<u>H</u>); ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.2 (C=O), 141.7 (CH), 137.6 (C), 61.6 (C), 59.0 (CH_2), 57.1 (CH), 16.4 (CH_3), 11.1 (CH_3); HRMS (TOF MS ASAP+) *m/z calc*. for $C_{15}H_{19}O_2$: 231.1385 $[M+H]^+$ found: 231.1381.

1,2,3,4,9-Pentamethyl-1,4,4a,8a-tetrahydro-1,4-methan-naphthalene-5,8-dione 3.1h[31]



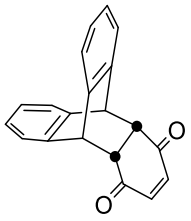
3.1h

1,2,3,4,5-Pentamethylcyclopentadiene **3.10h** (391 µL, 2.50 mmol, 1.0 equiv.) was added to a flask containing *p*-benzoquinone **3.11** (270.9 mg, 2.50 mmol, 1.0 equiv.), methyltrioxorhenium (6.2 mg, 0.025 mmol, 0.01 equiv.) and acetone (1 mL). The reaction mixture was stirred at room temperature for 45 minutes. The solvent was then removed by reduced pressure and the crude mixture was recrystallised in hot hexanes to yield **3.1g** (600.9 mg, 2.46 mmol, 98%, 6:1 d.r.). Further purification was carried out by silica gel column chromatography (20:1 toluene:DCM → 10:1 toluene:DCM) to yield **3.1g** (65.0 mg, 0.26 mmol, 11 %, 20:1 d.r.) as a yellow powder.

Mp = 125-128 °C (Toluene/DCM); R_f = 0.57 in 3:1 petroleum ether:EtOAc; ν_{max}/ cm^{-1}:2694, 2927, 2869, 1730, 1660. 1440, 1381, 1115, 873; ^1H NMR (300 MHz, $CDCl_3$) δ 6.44 (s, 2H, =CH), 2.82 (s, 2H, CH), 1.41 (q, *J* = 6.4 Hz, 1H, C<u>H</u>CH_3), 1.34 (s, 6H, CH_3), 1.23 (s, 6H, CH_3), 0.58 (d, *J* = 6.4 Hz, 3H,CHC<u>H</u>$_3$); ^{13}C NMR (101 MHz, $CDCl_3$)

δ 199.2 (C), 141.9 (CH), 133.9 (C), 62.8 (CH), 61.9 (C), 57.1 (CH), 14.1 (CH_3), 11.4 (CH_3), 7.5 (CH_3).

9,10-Dihydro-9,10-[1,2]benzenoanthracene-13,16-dione 3.1i[40]

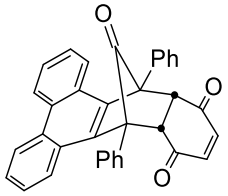


3.1i

To an oven dried reflux apparatus, back-filled with argon, *p*-benzoquinone **3.11** (301.0 mg, 2.50 mmol, 1.00 equiv.) was dissolved in xylenes **3.10i** (5 mL) and stirred for 5 minutes before anthracene was added to the reaction (300.0 mg, 2.80 mmol, 1.10 equiv.). The reaction was stirred at reflux for 16 h. The reaction was cooled, and the crude product filtered and washed with cold xylenes. The crude product was recrystallised in hot xylenes to yield **3.1i** (530.2 mg, 1.86 mmol, 74%) as a yellow powder.

Mp: 219-221 °C (xylenes) (literature mp: 231-233 °C)[40]; R_f: 0.36 in 5:1 petroleum ether:EtOAc; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 – 7.36 (m, 2H, Ar-H), 7.23 – 7.15 (m, 4H, Ar-H), 7.11 – 7.05 (m, 2H, Ar-H), 6.31 (s, 2H, =CH), 4.87 (app. t, *J* = 1.3 Hz, 2H, C<u>H</u>Ar), 3.14 (app. t, *J* = 1.3 Hz, 2H, CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.5 (C), 141.7 (C), 140.7 (CH), 139.8 (C), 126.9 (CH), 126.8 (CH), 124.9 (CH), 124.0 (CH), 49.2 (CH), 49.1 (CH); HRMS (TOF MS ASAP+) *m/z calc.* for $C_{20}H_{13}O_2$: 285.0916 $[M-H]^+$ found: 285.0916.

9,14-Diphenyl-9,9a,13a,14-tetrahydro-9,14-methanobenzo[f]tetraphene-10,13,15-trione 3.1j[41]

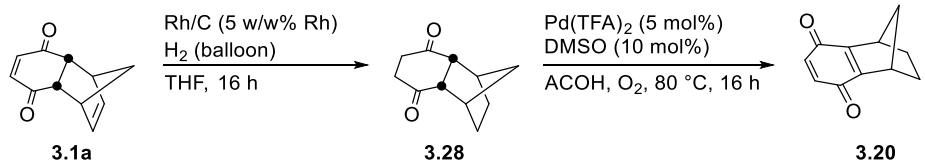


3.1j

Phencyclone **3.10j** (290.0 mg, 0.5 mmol, 1.0 equiv.) was added to reflux apparatus containing *p*-benzoquinone **3.11** (80.0 mg, 0.75 mmol, 1.5 equiv.) and benzene (5 mL) and stirred at reflux for 16 h. The solvent was then removed under reduced pressure and the resulting crude was recrystallised from hot $CHCl_3$ to yield **3.1j** (215.4 mg, 0.44 mmol, 88% yield) as a pale yellow powder.

Mp: decomp. 265-268 °C ($CHCl_3$) (Literature: 278-282 °C)[41]; R_f: 0.1 in 5:1 petroleum ether:EtOAc; ν_{max}/ cm^{-1}: 3027, 1787, 1687, 1603, 1582, 1567, 1498, 1447, 750, 726, 698; ^1H NMR (300 MHz, $CDCl_3$) δ 8.69 (d, *J* = 8.4 Hz, 2H, Ar-H), 8.29 (d, *J* = 7.6 Hz, 2H, Ar-H), 7.67 (td, *J* = 7.6, 1.5 Hz, 2H, Ar-H), 7.58 (ddd, *J* = 8.4, 6.8, 1.5 Hz, 2H, Ar-H), 7.48 (tt, *J* = 7.6, 1.2 Hz, 2H, Ar-H), 7.36 (td, *J* = 7.6, 1.5 Hz, 2H, Ar-H), 7.27 (td, *J* = 8.4, 1.2 Hz, 2H, Ar-H), 7.19 (dd, *J* = 8.4, 1.5 Hz, 2H, Ar-H), 7.09 (dt, *J* = 8.0, 1.5 Hz, 2H, Ar-H), 5.76 (s, 2H, =CH), 4.62 (s, 2H, CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.2 (C), 194.9 (C), 141.7 (CH), 134.2 (C), 133.4 (C), 131.35 (CH), 131.32 (C), 129.1 (CH), 128.5 (CH), 128.35 (CH), 128.32 (CH), 127.3 (CH), 126.9 (CH), 126.5 (C), 126.2 (CH), 123.4 (CH), 65.7 (C), 48.3 (CH).

1,2,3,4-Tetrahydro-1,4-methanonaphthalene-5,8-dione 3.20



Diels-Alder adduct **3.1a** (675.5 mg, 3.90 mmol, 1.0 equiv.) was added to a flask charged with Rh/C (5 w/w%, 58.8 mg, 0.03 mmol, 0.01 equiv.) and THF (10 mL). The flask was sealed with a septum and H_2 was backfilled into the flask *via* balloon (3 times). The reaction was stirred at room temperature under an atmosphere of H_2 (balloon) for 16 h. The reaction was filtered through a pad of celite to remove catalyst and washed with EtOAc (3 × 10 mL). Solvent was removed under reduced pressure. The resulting crude mixture was purified by silica gel column chromatography (3:1 petroleum ether:EtOAc) to yield **3.28** (348.5 mg, 2.0 mmol, 50%) as a colourless oil.

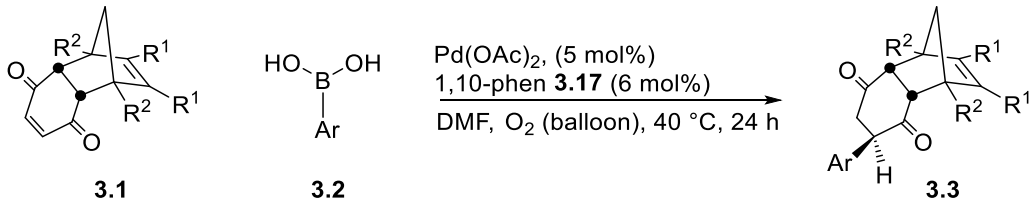
R_f: 0.2 in 3:1 petroleum ether:EtOAc; ν_{max}/ cm^{-1}:2991, 2906, 1701, 1308, 1152, 932; ^1H NMR (300 MHz, $CDCl_3$) δ = 2.96 – 2.91 (m, 2H, CH), 2.86 – 2.82 (m, 2H, Ar-H, CH), 2.82 – 2.71 (m, 2H, C<u>H</u>H), 2.56 – 2.41 (m, 2H, CH<u>H</u>), 1.58 – 1.46 (m, 2H, CH_2), 1.46 – 1.37 (m, 2H, CH_2), 1.36 – 1.25 (m, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 210.2 (C), 52.2 (CH), 41.7 (CH), 39.2 (CH_2), 38.8 (CH_2), 24.7 (CH_2); HRMS (TOF MS EI +) *m/z calc.* for $C_{11}H_{12}O_2$: 176.0837 $[M-2H]^+$; found: 176.0839.

3.28 (53.9 mg, 0.3 mmol, 1.0 equiv.) was added to reflux apparatus containing $Pd(TFA)_2$ (5.0 mg, 0.015 mmol, 0.05 equiv.), DMSO (2.0 µL, 0.03 mmol, 0.1 equiv.) and glacial acetic acid (1.5 mL). The reaction was stirred at 80 °C under an atmosphere of O_2 (balloon) for 16 h. Solvent was then removed under reduced pressure. The resulting crude was purified by silica gel column chromatography (10:1 petroleum ether:EtOAc) to yield **3.20** (44.0 mg, 0.25 mmol, 85%) as a yellow oil.

R_f: 0.2 in 10:1 petroleum ether:EtOAc; ν_{max}/ cm^{-1}: 2951, 2876, 1645, 1578, 1448, 1323, 944, 834; ^1H NMR (300 MHz, $CDCl_3$) δ = 6.57 (s, 2H, =CH), 3.48 (dq, *J* = 3.0, 1.7 Hz, 2H, CH), 1.96 – 1.88 (dm, *J* = 12.1 Hz, 2H, CHH), 1.63 (dt, *J* = 9.1, 1.7 Hz, 1H, CHH), 1.40 (dt, *J* = 9.1, 1.4 Hz, 1H, CHH), 1.17 (ddd, *J* = 12.1, 4.2, 2.3 Hz, 2H, CHH), ^{13}C NMR (75 MHz, $CDCl_3$) δ = 184.5 (C), 151.7 (C), 136.3 (CH), 47.9 (CH_2), 40.7 (CH), 25.1 (CH_2); HRMS (TOF MS ASAP +) *m/z calc.* for $C_{11}H_{11}O_2$: 175.0759 $[M-H]^+$; found: 175.0759.

3.9.3 Conjugate Addition General Reaction Procedures

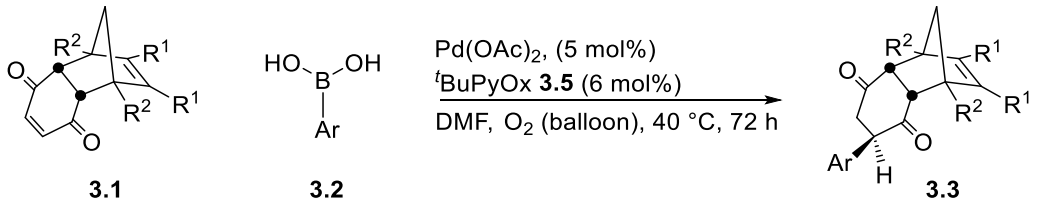
General Racemic Reaction Procedure



3.1 **3.2** **3.3**

To a round-bottom flask, dried and back-filled with oxygen (*via* balloon), Diels-Alder adduct **3.1** (0.10 mmol, 1.0 equiv.), boronic acid **3.2** (0.24 mmol, 2.4 equiv.), $Pd(OAc)_2$ (1.1 mg, 0.005 mmol, 0.05 equiv.) and 1,10-phenanthroline **3.17** (1.1 mg, 0.006 mmol, 0.05 equiv.) were stirred in DMF (1.0 mL) at 40 °C under an atmosphere of oxygen (balloon) for 24 h. The reaction was then diluted with 2:1 Et_2O:EtOAc (15 mL) and the organic layer was washed with H_2O (3 × 10 mL) and brine (1 × 10 mL). The combined organic layers were dried over $MgSO_4$ and solvent was removed under reduced pressure. The resulting crude was purified by silica gel column chromatography and separating conditions were determined by chiral stationary phase HPLC.

General Enantioselective Reaction Procedure A

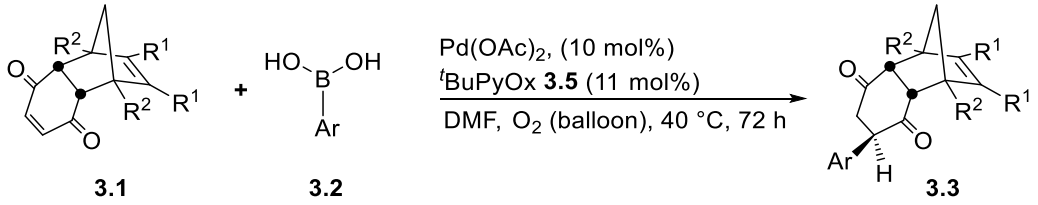


3.1 3.2 3.3

To a round-bottom flask, dried and back-filled with oxygen (*via* balloon), $Pd(OAc)_2$ (1.1 mg, 0.005, 0.05 equiv.) and ^{t}BuPyOx **3.5** (1.2 mg, 0.006 mmol, 0.06 equiv.) were premixed in DMF (0.3 mL) for approx. 30 minutes at room temperature. Diels-Alder adduct **3.1** (0.10 mmol, 1.0 equiv.) and boronic acid **3.2** (0.24 mmol, 2.4 equiv.) were then added, along with DMF (0.7 mL) and the reaction was stirred at 40 °C under an atmosphere of oxygen (balloon) for 72 h. The reaction was then diluted with 2:1 Et_2O:EtOAc (15 mL) and the organic layer was washed with H_2O (3 × 10 mL) and brine (1 × 10 mL), the combined organic layers were dried over $MgSO_4$ and solvent was removed under reduced pressure. The resulting crude was purified by silica gel column chromatography and enantiomeric ratios were determined by chiral stationary phase HPLC.

General Enantioselective Reaction Procedure B

In instances where the product and starting material had the same R_f value, the reaction was carried out under an increased ligand and catalyst loading to ensure the reaction went to completion (so that an isolated yield could be obtained).

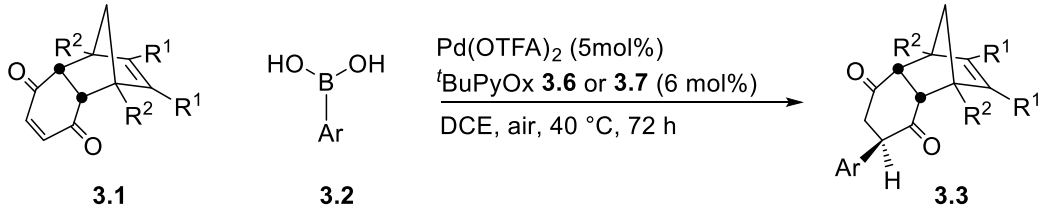


3.1 3.2 3.3

To a round-bottom flask, dried and back-filled with oxygen (*via* balloon), $Pd(OAc)_2$ (2.2 mg, 0.010, 0.10 equiv.) and ^{t}BuPyOx **3.5** (2.2 mg, 0.011 mmol, 0.11 equiv.) were

premixed in DMF (0.3 mL) for approx. 30 minutes at room temperature. Diels-Alder adduct **3.1** (35.4 mg, 0.0999 mmol, 1.0 equiv.) and boronic acid **3.2** (0.24 mmol, 2.4 equiv.) were then added, along with DMF (0.7 mL) and the reaction was stirred at 40 °C under an atmosphere of oxygen (balloon) for 72 h. The reaction was then diluted with 2:1 Et_2O:EtOAc (15 mL) and the organic layer was washed with H_2O (3 × 10 mL) and brine (1 × 10 mL), the combined organic layers were dried over $MgSO_4$ and solvent was removed under reduced pressure. The resulting crude was purified by silica gel column chromatography and enantiomeric ratios were determined by chiral stationary phase HPLC.

General enantioselective procedure C

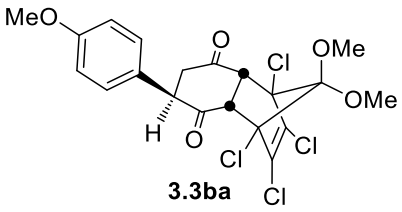


3.1 **3.2** **3.3**

To an oven dried 4 mL vial, $Pd(OTFA)_2$ (1.7 mg, 0.005, 0.05 equiv.) and 4/5-CF_3^{t}BuPyOx **3.6** or **3.7** (0.006 mmol, 0.06 equiv.) were pre-mixed in DCE (0.3 mL) for approx. 30 minutes at room temperature. Diels-Alder adduct **3.1** (0.10 mmol, 1.0 equiv.) and boronic acid **3.2** (0.24 mmol, 2.4 equiv.) were then added, along with DCE (0.2 mL). The vial was sealed and the reaction was stirred at 40 °C for 72 h. The reaction was then filtered through a silica plug in a Pasteur pipette using DCM (15 mL) and solvent was then removed under reduced pressure. The resulting crude was purified by silica gel column chromatography and enantiomeric ratios were determined by chiral stationary phase HPLC.

3.9.4 Diels-Alder Adduct 3.1 Scope

1,2,3,4-Tetrachloro-9,9-dimethoxy-6-(4-methoxyphenyl)-hexahydro-1,4-methanonaphthalene-5,8-dione 3.3ba



3.3ba

Racemic procedure:

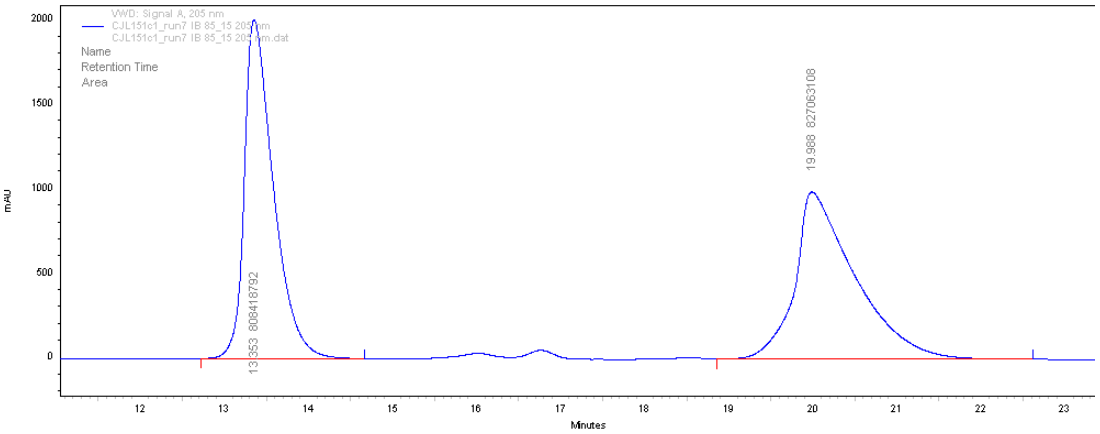
General racemic procedure was followed with modifications, reacting *p*-methoxyphenyl boronic acid **3.2a** (37.0 mg, 0.25 mmol, 2.5 equiv.), Diels-Alder Adduct **3.1b** (37.0 mg, 0.099 mmol, 1.0 equiv.), $Pd(OAc)_2$ (1.1 mg, 0.005 mmol, 0.01 equiv.) and 1,10-phenanthroline **3.17** (1.1 mg, 0.006 mmol, 0.012 equiv.) in DMF (1.0 mL) under at an atmosphere of O_2 at 30 °C for 24 h. The resulting crude was purified by silica gel column chromatography (hexane/EtOAc 5:1) to yield **3.3ba** (35.0 mg, 0.074 mmol, 74%, >20:1) as a white crystalline solid.

Enantioselective procedure:

General enantioselective procedure A was followed, reacting *p*-methoxyphenyl boronic acid **3.2a** (37.3 mg, 0.25 mmol, 2.5 equiv.), Diels-Alder adduct **3.1b** (39.6 mg, 0.099 mmol, 1.0 equiv.), $Pd(OAc)_2$ (1.1 mg, 0.005 mmol, 0.01 equiv.) and ^{t}BuPyOx **3.5** (1.2 mg, 0.006 mmol, 0.012 equiv.) in DMF (1.0 mL) under an atmosphere of O_2 at 30 °C for 72 h. The resulting crude was purified by silica gel column chromatography (hexanes/EtOAc 5:1) to yield **3.3ba** (29.9 mg, 0.063 mmol, 80%, >20:1 d.r., 92:8 e.r.) as an off-white crystalline solid.

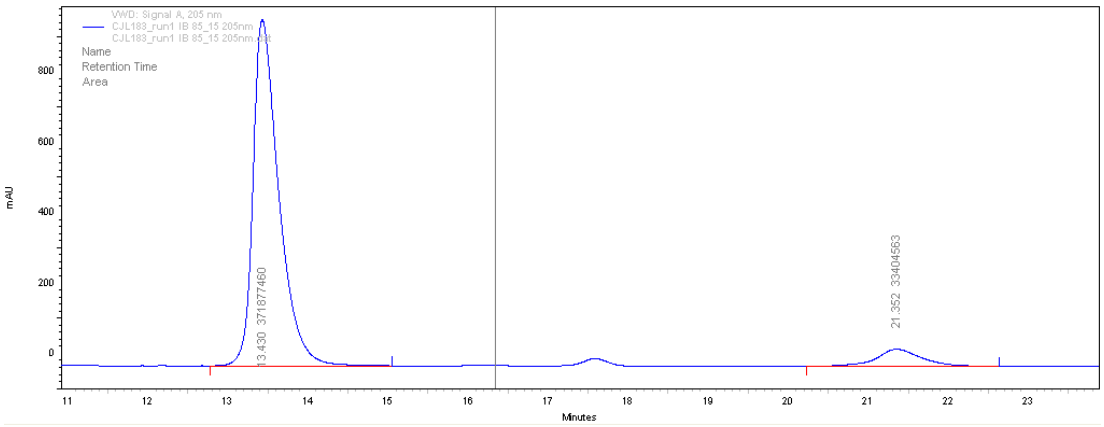
Mp: 139 -141 °C (hexanes/chloroform); R_f: 0.28 in 3:1 petroleum ether:EtOAc; ν_{max}/ cm^{-1}: 2956, 2863, 1716, 1612, 1596, 1514, 1250, 1189, 1120, 844, 808, 720; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.00 – 6.93 (d, *J* = 9.0 Hz, 2H, Ar-H), 6.82 (d, *J* = 9.0 Hz, 2H, Ar-

H), 3.73 (s, 3H, OCH_3), 3.65 (dd, *J* = 9.0, 4.9 Hz, 1H, C<u>H</u>Ar), 3.60 (d, *J* = 10.0 Hz, 1H, CH), 3.51 (s, 3H, OCH_3), 3.51 (s, 3H, OCH_3), 3.48 (d, 10.0 Hz, 1H, CH), 3.05 (dd, *J* = 16.0, 9.0 Hz, 1H, C<u>H</u>H), 2.65 (dd, *J* = 16.0, 4.9 Hz, 1H, CH<u>H</u>).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.2 (C), 202.1 (C), 159.6 (C), 130.8 (C), 130.5 (C), 128.9 (CH), 126.4 (C), 114.8 (CH), 111.5 (C), 76.58 (C), 76.55 (C), 57.0 (CH), 56.3 (CH), 55.5 (CH_3), 53.4 (CH_3), 52.3 (CH_3), 52.2 (CH), 43.8 (CH_2). HRMS (TOF MS ASAP +) *m/z calc.* for $C_{20}H_{19}O_5Cl_4$: 478.9987 $[M+H]^+$; found: 478.9984; $[\alpha]_D^{21.0}$ = + 4.8 (c 0.5 , $CHCl_3$); 92:8 e.r.; HPLC (CHIRALPAK IB, hexane/2-propanol: 85:15, flow rate: 1.0 mL min^{-1}, detection UV 205 nm, 25 °C) t_R of major isomer: 13.43 min, t_R of minor isomer: 21.35 min.



VWD: Signal A, 205 nm Results

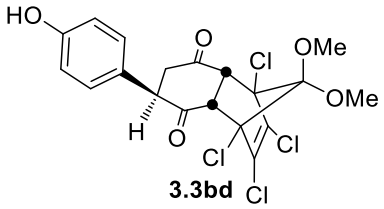
Retention Time	Area	Area %	Height	Height %
13.353	808418792	49.43	33660470	66.94
19.988	827063108	50.57	16621854	33.06
Totals	1635481900	100.00	50282324	100.00



VWD: Signal A, 205 nm Results

Retention Time	Area	Area %	Height	Height %
13.430	371877460	91.76	16487966	95.25
21.352	33404563	8.24	821618	4.75
Totals	405282023	100.00	17309584	100.00

1,2,3,4-Tetrachloro-6-(4-hydroxyphenyl)-9,9-dimethoxy-1,4,4a,6,7,8a-hexahydro-1,4-methanonaphthalene-5,8-dione 3.3bd



3.3bd

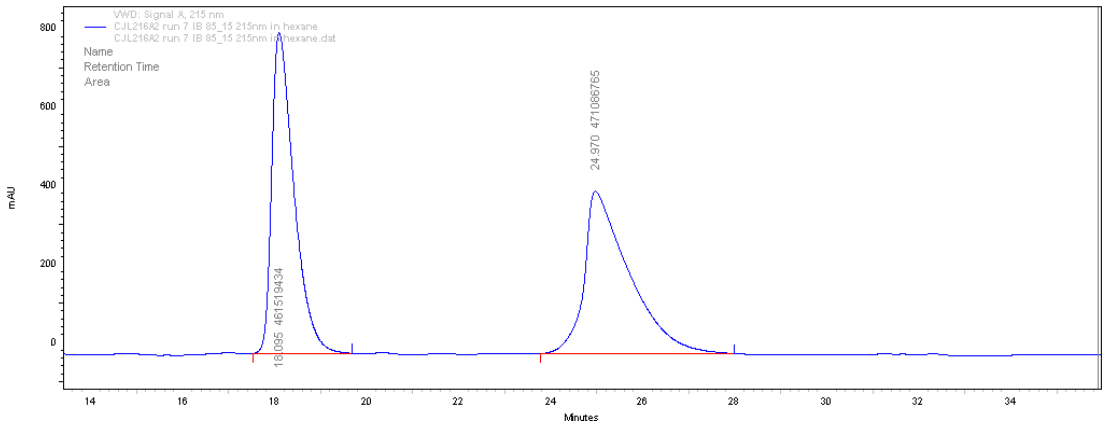
Racemic procedure:

General racemic procedure was followed with modifications, reacting *p*-hydroxyphenyl boronic acid **3.2d** (33.1 mg, 0.24 mmol, 2.4 equiv.), Diels-Alder Adduct **3.1b** (37.0 mg, 0.099 mmol, 1.0 equiv.), $Pd(OAc)_2$ (1.1 mg, 0.005 mmol, 0.01 equiv.) and 1,10-phenanthroline **3.17** (1.1 mg, 0.006 mmol, 0.012 equiv.) in DMF (1.0 mL) under an atmosphere of O_2 at 40 °C for 24 h. The resulting crude was purified by silica gel column chromatography (hexane/EtOAc 20:1 → 3:1) to yield **3.3bd** (38.7 mg, 0.083 mmol, 83%, >20:1) as a white crystalline solid.

Enantioselective procedure:

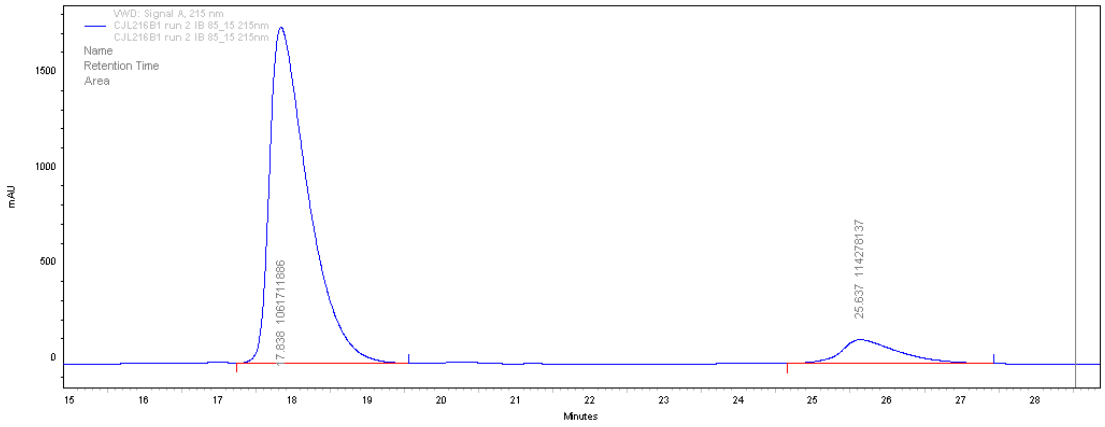
General enantioselective procedure A was followed, reacting *p*-hydroxyphenyl boronic acid **3.2d** (33.1 mg, 0.24 mmol, 2.4 equiv.), Diels-Alder adduct **3.1b** (39.6 mg, 0.099 mmol, 1.0 equiv.), $Pd(OAc)_2$ (1.1 mg, 0.005 mmol, 0.01 equiv.) and ^{t}BuPyOx **3.5** (1.2 mg, 0.006 mmol, 0.012 equiv.) in DMF (1.0 mL) under at an atmosphere of O_2 at 40 °C for 72 h. The resulting crude was purified by silica gel column chromatography (hexanes/EtOAc 5:1 → 3:1) to yield **3.3bd** (30.0 mg, 0.065 mmol, 65%, >20:1 d.r., 90:10 e.r.) as an off-white crystalline solid.

Mp: 191-192 °C (hexanes/chloroform); R_f: 0.2 in 3:1 petroleum ether:EtOAc; ν_{max}/ cm^{-1}: 3455, 2955, 1720, 1705, 1614, 1596, 518, 1439, 1188, 1126, 847, 808, 751; ^{1}H NMR (300 MHz, $CDCl_3$) ; δ 6.99 (d, *J* = 8.7 Hz, 2H, Ar-H), 6.82 (d, *J* = 8.7 Hz, 1H, Ar-H), 4.82 (s, 1H, OH), 3.71 (dd, *J* = 9.2, 4.8 Hz, 1H, C<u>H</u>Ar), 3.67 (d, *J* = 9.9 Hz, 1H, CH), 3.59 (s, 3H, OCH_3), 3.58 (s, 3H, OCH_3), 3.56 (d, *J* = 9.9 Hz, 1H, CH), 3.11 (dd, *J* = 16.0, 9.2 Hz, 1H, C<u>H</u>H), 2.73 (dd, *J* = 16.0, 4.8 Hz, 1H, CH<u>H</u>); ^{13}C NMR (101 MHz, $CDCl_3$) 202.2 (C), 202.1 (C), 177.4 (C), 155.6 (C), 130.8 (C), 130.6 (C), 129.1 (CH), 126.7 (C), 116.3 (CH), 111.6 (C), 76.6 (C), 57.1 (CH), 56.3 (CH), 53.4 (CH_3), 52.3 (CH_3), 52.2 (CH), 43.9 (CH_2); HRMS (TOF MS ASAP +) *m/z calc.* for $C_{19}H_{17}O_5Cl_4$: 464.9830 $[M+H]^+$; found: 464.9825; $[\alpha]_D^{20.7}$ = + 26.4 (c 1.67 , $CHCl_3$); 90:10 e.r.; HPLC (CHIRALPAK IB, hexane/2-propanol: 85:15, flow rate: 1.0 mL min^{-1}, detection UV 205 nm, 25 °C) t_R of major isomer: 17.84 min, t_R of minor isomer: 25.64 min.



VWD: Signal A, 215 nm Results

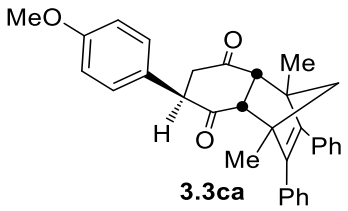
Retention Time	Area	Area %	Height	Height %
18.095	461519434	49.49	13715473	66.39
24.970	471086765	50.51	6942893	33.61
Totals	932606199	100.00	20658366	100.00



VWD: Signal A, 215 nm Results

Retention Time	Area	Area %	Height	Height %
17.838	1061711886	90.28	29508416	93.35
25.637	114278137	9.72	2103016	6.65
Totals	1175990023	100.00	31611432	100.00

6-(4-Methoxyphenyl)-1,4-dimethyl-2,3-diphenyl-1,4,4a,6,7,8a-hexahydro-1,4-methanonaphthalene-5,8-dione 3.3ca



3.3ca

Racemic procedure:

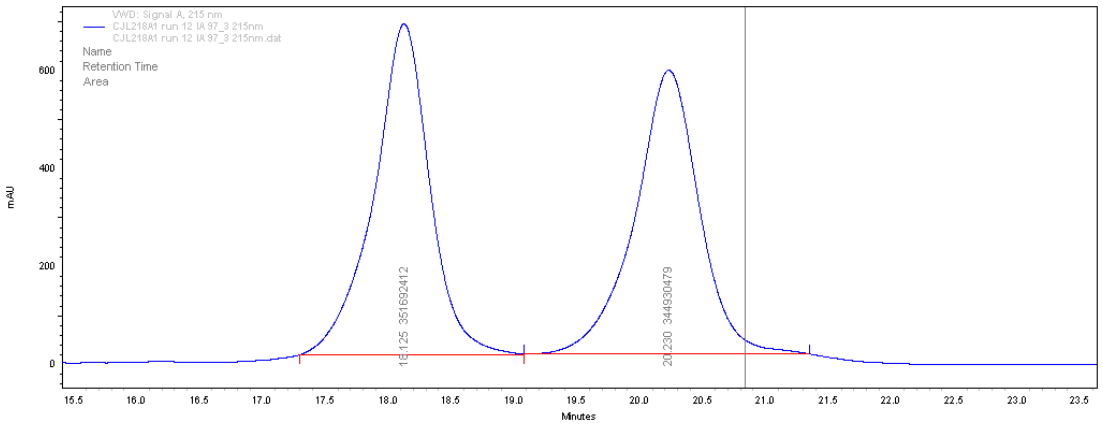
General racemic procedure was followed, reacting *p*-methoxybenzene boronic acid **3.2a** (36.5 mg, 0.24 mmol, 2.4 equiv.), Diels-Alder adduct **3.1c** (35.4 mg, 0.099 mmol, 1 equiv.), $Pd(OAc)_2$ (1.1 mg, 0.005 mmol, 0.05 equiv.) and 1,10-phenanthroline **3.17** (1.1 mg, 0.006 mmol, 0.06 equiv.) in DMF (1 mL) under an atmosphere of O_2 (balloon) at 40 °C for 24 h.. The resulting crude was purified by silica gel column chromatography (20:1 toluene/EtOAc) to yield **3.3ca** (39.3 mg, 0.085 mmol, 85%, >20:1 d.r.) as a colourless crystalline solid.

Enantioselective procedure:

General enantioselective procedure A was followed, reacting *p*-methoxyphenyl boronic acid **3.2a** (36.5 mg, 0.24 mmol, 2.4 equiv.) with Diels-Alder adduct **3.1c** (35.4 mg, 0.099 mmol, 1 equiv.) $Pd(OAc)_2$ (1.1 mg, 0.005 mmol, 0.05 equiv.) and ^{t}BuPyOx **3.5** (1.2 mg, 0.006 mmol, 0.06 equiv.) in DMF (1 mL) under an atmosphere of O_2 (balloon) at 40 °C for 72 h. The resulting crude was purified by silica gel column chromatography (10:1 → 3:1 petroleum ether/EtOAc) to yield **3.3ca** (32.3 mg, 0.070 mmol, 70%, >20:1 d.r., 97:3 e.r.) as a colourless crystalline solid.

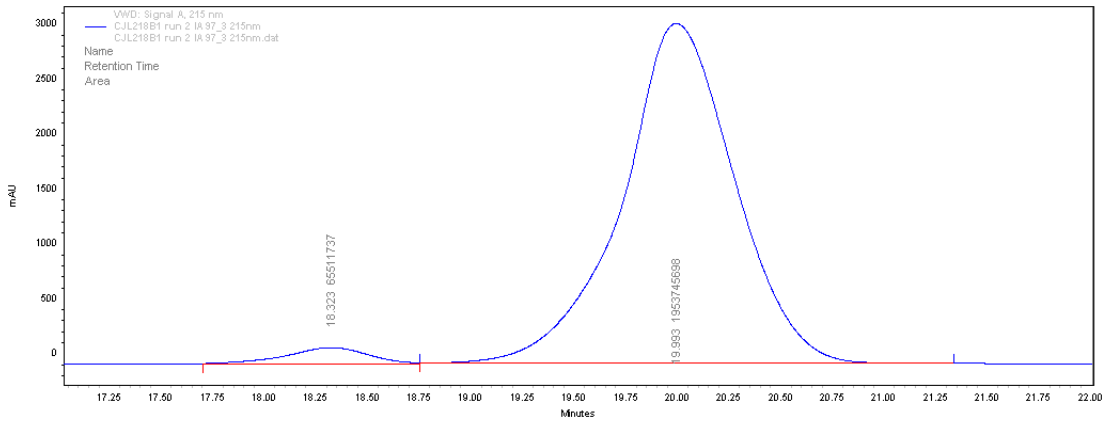
Mp: 158 °C (DCM/petrol ether); R_f: 0.3 in 5:1 petroleum ether:EtOAc; ν_{max}/ cm^{-1}: 2960, 1932, 1699, 1611, 1514, 1471, 1248, 823, 743, 696; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 – 7.11 (m, 6H, Ar-H), 7.04 – 6.83 (m, 8H, Ar-H), 3.88 (dd, *J* = 10.2, 5.1 Hz, 1H, C<u>H</u>Ar), 3.79 (s, 3H, OMe), 3.28 (d, *J* = 9.9 Hz, 1H, CH), 3.19 (d, *J* = 9.9 Hz, 1H, CH), 3.06 (dd,

J = 16.0, 10.1 Hz, 1H, C<u>H</u>H), 2.80 (dd, *J* = 16.0, 5.1 Hz, 1H, CH<u>H</u>), 1.83 (d, *J* = 8.5 Hz, 1H, C<u>H</u>H), 1.62 (s, 3H, CH_3), 1.58 (d, *J* = 8.5 Hz, 1H, CH<u>H</u>), 1.54 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.68 (C), 208.66 (C), 159.2 (C), 147.4 (2×C), 145.0 (C), 135.7 (C), 135.5 (C), 129.4 (CH), 129.3 (CH), 129.2 (CH), 128.3 (CH), 128.1 (CH), 127.1 (CH), 114.5 (CH), 66.2 (CH_2), 60.2 (CH), 59.0 (CH), 58.13 (C), 58.10 (C), 55.4 (CH_3), 52.2 (CH), 45.4 (CH_2), 19.1 (CH_3), 18.8 (CH_3) with 1 overlapping aromatic CH signal; HRMS (FTMS + p NSI) *m/z calc*. for $C_{32}H_{34}O_3N$: 480.2533 $[M+NH_4]^+$; found:480.2526; $[\alpha]_D^{20.1}$ = +12.0 (*c* 0.5, $CHCl_3$); 97:3 e.r.; HPLC (CHIRALPAK IA, hexane/2-propanol: 97:3, flow rate: 1.0 mL min^{-1}, detection UV 215 nm, 25 °C) t_R of major isomer: 18.32 min, t_R of minor isomer: 19.99 min.



VWD: Signal A, 215 nm Results

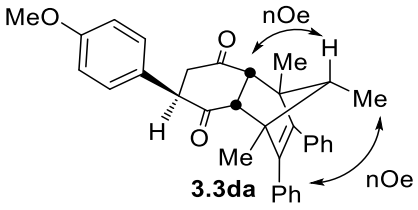
Retention Time	Area	Area %	Height	Height %
18.125	351692412	50.49	11332086	53.83
20.230	344930479	49.51	9719160	46.17
Totals	696622891	100.00	21051246	100.00



VWD: Signal A, 215 nm Results

Retention Time	Area	Area %	Height	Height %
18.323	65511737	3.24	2429415	4.48
19.993	1953745698	96.76	51836693	95.52
Totals	2019257435	100.00	54266108	100.00

6-(4-Methoxyphenyl)-1,4,9-trimethyl-2,3-diphenyl-1,4,4a,6,7,8a-hexahydro-1,4-methanonaphthalene-5,8-dione 3.3da



Major diastereomer confirmed by NOESY 2D NMR.

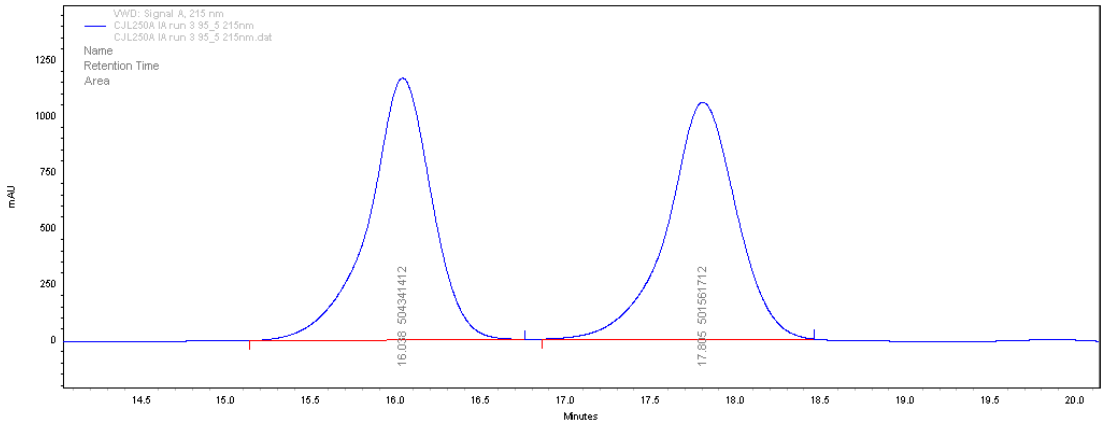
Racemic procedure:

General racemic procedure was followed with modifications and on a reduced scale, reacting *p*-methoxyphenyl boronic acid **3.2a** (18.4 mg, 0.12 mmol, 2.4 equiv.), Diels-Alder adduct **3.1d** (18.4 mg, 0.050 mmol, 1.0 equiv., 7:1 d.r.), $Pd(OAc)_2$ (1.1, 0.010 mmol, 0.10 equiv.) and 1,10-phenanthroline **3.17** (1.1 mg, 0.012 mmol, 0.12 equiv.) in DMF (0.5 mL) under an atmosphere of O_2 at 40 °C for 24 h. The resulting crude was purified by silica gel column chromatography (hexane:EtOAc 10:1 → 8:1) to yield **3.3da** (13.6 mg, 0.057 mmol, 57%, >20:1 d.r.) as an off-white powder.

Enantioselective procedure:

General enantioselective procedure B was followed with modifications on a reduced scale, reacting *p*-methoxyphenyl boronic acid **3.2a** (18.4 mg, 0.12 mmol, 2.4 equiv.), Diels-Alder adduct **3.1d** (18.4 mg, 0.05 mmol, 1.0 equiv., 7:1 d.r.), $Pd(OAc)_2$ (1.1 mg, 0.010 mmol, 0.05 equiv.) and ^{t}BuPyOx **3.5** (1.2 mg, 0.012 mmol, 0.12 equiv.) in DMF (0.5 mL) at 40 °C for 72 h. The resulting crude was purified by silica gel column chromatography (hexane:EtOAc 20:1 → 5:1) to yield **3.3da** (17.3 mg, 0.073 mmol, 73%, >20:1 d.r., 93:7 e.r.) as a white powder solid.

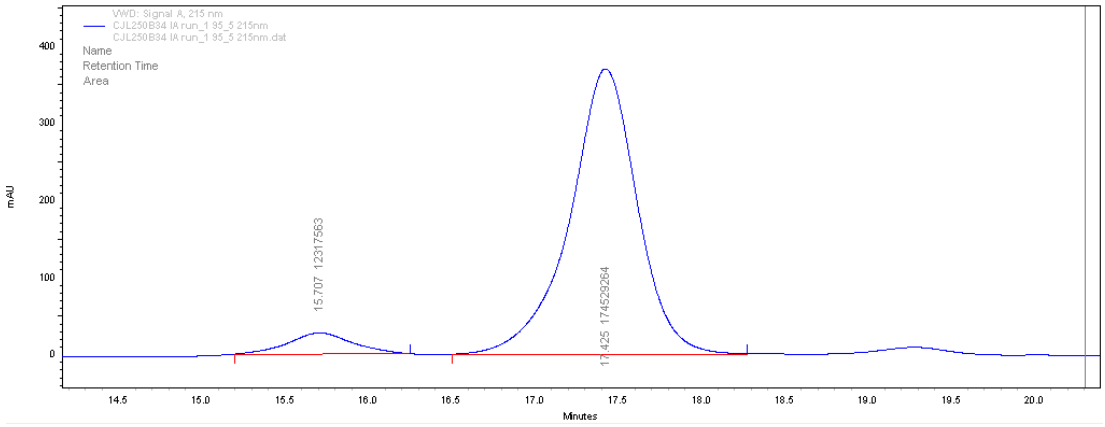
Mp: 75-77 °C (hexane/chloroform); R_f: 0.2 in 10:1 petroleum ether:EtOAc; ν_{max}/ cm^{-1}: 2960, 2924, 1700, 1612, 1516, 1489 1249, 1121, 742, 697; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 – 7.11 (m, 6H, Ar-H), 7.01 (d, *J* = 8.5 Hz, 2H, Ar-H), 6.95 – 6.82 (m, 6H, Ar-H), 3.90 (dd, *J* = 10.3, 5.1 Hz, 1H, C<u>H</u>Ar), 3.80 (s, 3H, OCH_3), 3.21 (d, *J* = 9.8 Hz, 1H, CH), 3.13 (d, *J* = 9.8 Hz, 1H, CH), 3.11 (dd, *J* = 16.0, 10.3 Hz, 1H, C<u>H</u>H).2.81 (dd, *J* = 16.0, 5.1 Hz, 1H, CH<u>H</u>), 1.71 (q, *J* = 6.3 Hz, 1H, C<u>H</u>CH_3), 1.48 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 0.93 (d, *J* = 6.3 Hz, 3H, CHC<u>H</u>$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.8 (C), 208.7 (C), 159.1 (C), 144.0 (C), 143.5 (C), 136.1 (C), 135.9 (C), 129.2 (CH), 129.0 (CH), 128.3 (CH), 128.19 (C), 128.15 (CH), 127.0 (CH), 114.4 (CH), 66.6 (CH), 61.1 (C), 60.2 (CH), 59.0 (CH), 55.4 (CH_3), 52.3 (CH), 45.5 (CH_2), 16.7 (CH_3), 16.4 (CH_3), 7.7 (CH_3), 1 × overlapping C signal, 2 × overlapping CH signals; HRMS (TOF MS ASAP +) *m/z calc.* for $C_{33}H_{31}O3$: 475.2273 $[M-H]^+$; found: 475.2269; $[\alpha]_D^{20.5}$ = + 20.0 (c 0.5 , $CHCl_3$); 97:3 e.r.; HPLC (CHIRALPAK IA, hexane/2-propanol: 95:5, flow rate: 1.0 mL min^{-1}, detection UV 215 nm, 25 °C) t_R of major isomer: 17.43 min, t_R of minor isomer: 15.71 min.



VWD: Signal A,
215 nm Results

Retention Time	Area	Area %	Height	Height %
16.038	504341412	50.14	19579235	52.50
17.805	501561712	49.86	17714000	47.50

Totals	1005903124	100.00	37293235	100.00

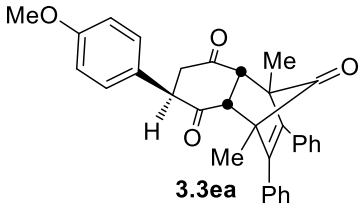


VWD: Signal A,
215 nm Results

Retention Time	Area	Area %	Height	Height %
15.707	12317563	6.59	458663	6.87
17.425	174529264	93.41	6212992	93.13

Totals	186846827	100.00	6671655	100.00

6-(4-Methoxyphenyl)-1,4-dimethyl-2,3-diphenyl-1,4,4a,6,7,8a-hexahydro-1,4-methanonaphthalene-5,8,9-trione 3.3ea



3.3ea

Racemic procedure:

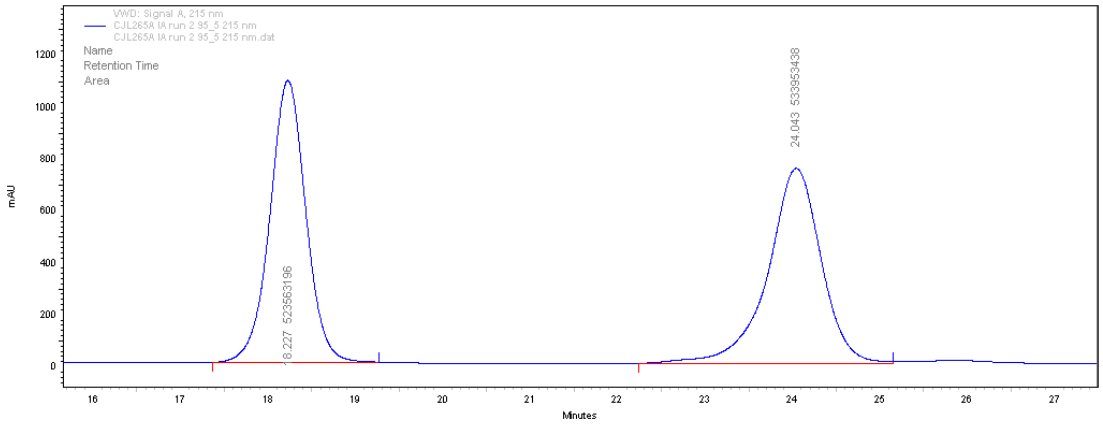
General racemic procedure was followed, reacting *p*-methoxyphenyl boronic acid **3.2a** (36.5 mg, 0.24 mmol, 2.4 equiv.), Diels-Alder adduct **3.1e** (38.6 mg, 0.099 mmol, 1.0 equiv.), $Pd(OAc)_2$ (1.1 mg, 0.005 mmol, 0.05 equiv.) and 1,10-phenanthroline **3.17** (1.1 mg, 0.006 mmol, 0.06 equiv.) in DMF (1.0 mL) under at atmosphere of O_2 (balloon) at 40 °C for 24 h. The resulting crude was purified by silica gel column chromatography (petroleum ether/EtOAc 20:1 → 5:1) to yield **3.3ea** (45.8 mg, 0.096 mmol, 96%, >20:1) as a white crystalline solid.

Enantioselective procedure:

General enantioselective procedure A was followed, reacting *p*-methoxyphenyl boronic **3.2a** (36.5 mg, 0.24 mmol, 2.4 equiv.), Diels-Alder adduct **3.1e** (38.6 mg, 0.099 mmol, 1.0 equiv.), $Pd(OAc)_2$ (1.1 mg, 0.005 mmol, 0.01 equiv.) and ^{t}BuPyOx **3.5** (1.2 mg, 0.006 mmol, 0.012 equiv.) in DMF (1.0 mL) under at an atmosphere of O2 at 40 °C for 72 h . The resulting crude was purified by silica gel column chromatography (petroleum ether/EtOAc 20:1 → 5:1) to yield **3.3ea** (32.3 mg, 0.068 mmol, 68%, >20:1 d.r., 94:6 e.r.) as a white crystalline solid.

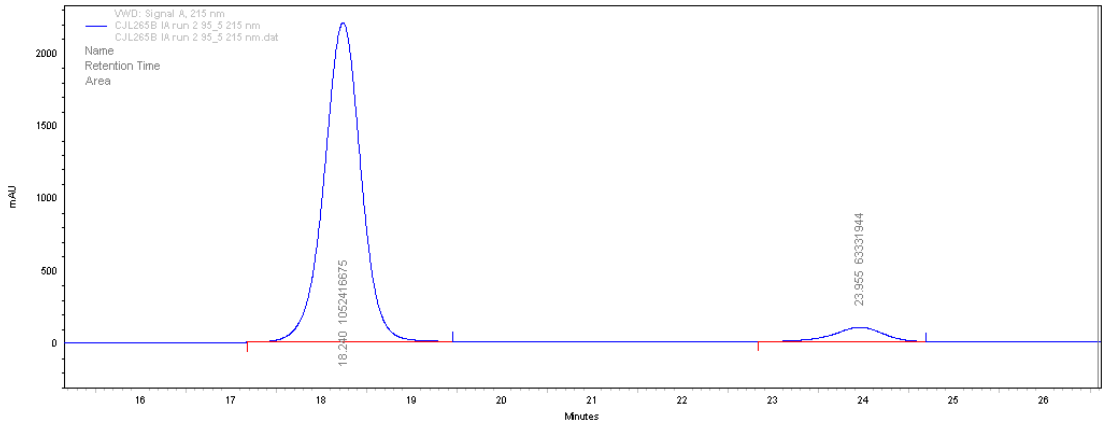
Mp: 156-158 °C; R_f: 0.2 in 5:1 petroleum ether:EtOAc; ν_{max}/ cm^{-1}: 2961, 2872, 1776, 1708, 1613, 1516, 1443, 1184, 780, 748, 698; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 – 7.16 (m, 6H, Ar-H), 7.05 – 6.99 (m, 2H, Ar-H), 6.95 – 6.87 (m, 6H, Ar-H), 3.89 (dd, *J* = 9.9, 4.9 Hz, 1H, C<u>H</u>Ar), 3.80 (s, 3H, OCH_3), 3.30 (d, *J* = 10.6 Hz, 1H, CH), 3.21 (d, *J* = 10.6 Hz, 1H, CH), 3.20 (dd, *J* = 15.9, 9.9 Hz, 1H, C<u>H</u>H), 2.85 (dd, *J* = 15.9, 4.9 Hz,

1H, CHH), 1.58 (s, 3H, CH_3), 1.52 (s, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.0 (C), 205.9 (C), 200.5 (C), 159.5 (C), 143.2 (C), 143.0 (C), 134.0 (C), 133.9 (C), 129.6 (CH), 129.4 (CH), 129.0 (CH), 128.5 (CH), 128.4 (CH), 127.9 (CH), 127.8 (CH), 127.2 (C), 114.7 (CH), 58.1 (C), 58.0 (C), 55.5 (CH_3), 55.1 (CH), 53.8 (CH), 52.6 (CH), 44.7 (CH_2), 12.4 (CH_3), 12.2 (CH_3); HRMS (TOF MS ASAP +) *m/z calc.* for $C_{32}H_{29}O_4$: 477.2066 $[M+H]^+$; found: 477.2063; $[\alpha]_D^{23.2}$ = + 46.6 (c 0.56, $CHCl_3$); 94:6 e.r.; HPLC (CHIRALPAK IA, hexane/2-propanol: 95:5, flow rate: 1.0 mL min^{-1}, detection UV 215 nm, 25 °C) t_R of major isomer: 18.24 min, t_R of minor isomer: 23.94 min.



VWD: Signal A, 215 nm Results

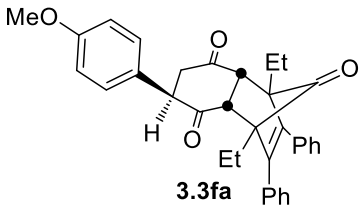
Retention Time	Area	Area %	Height	Height %
18.227	523563196	49.51	18259536	59.15
24.043	533953438	50.49	12610053	40.85
Totals	1057516634	100.00	30869589	100.00



VWD: Signal A, 215 nm Results

Retention Time	Area	Area %	Height	Height %
18.240	1052416675	94.32	36934338	95.71
23.955	63331944	5.68	1657386	4.29
Totals	1115748619	100.00	38591724	100.00

1,4-Diethyl-6-(4-methoxyphenyl)-2,3-diphenyl-1,4,4a,6,7,8a-hexahydro-1,4-methanonaphthalene-5,8,9-trione 3.3fa



3.3fa

Racemic procedure:

General racemic procedure was followed, reacting *p*-methoxyphenyl boronic acid **3.2a** (36.5 mg, 0.24 mmol, 2.4 equiv.), Diels-Alder adduct **3.1f** (39.6 mg, 0.099 mmol, 1.0 equiv.), $Pd(OAc)_2$ (1.1 mg, 0.005 mmol, 0.01 equiv.) and 1,10-phenanthroline **3.17** (1.1 mg, 0.006 mmol, 0.012 equiv.) in DMF (1.0 mL) under an atmosphere of O_2 at 40 °C for 24 h. The resulting crude was purified by silica gel column chromatography (petroleum ether/EtOAc 5:1) to yield **3.3fa** (49.2 mg, 0.097 mmol, 97%, >20:1 d.r.) as a white crystalline solid.

Enantioselective procedure:

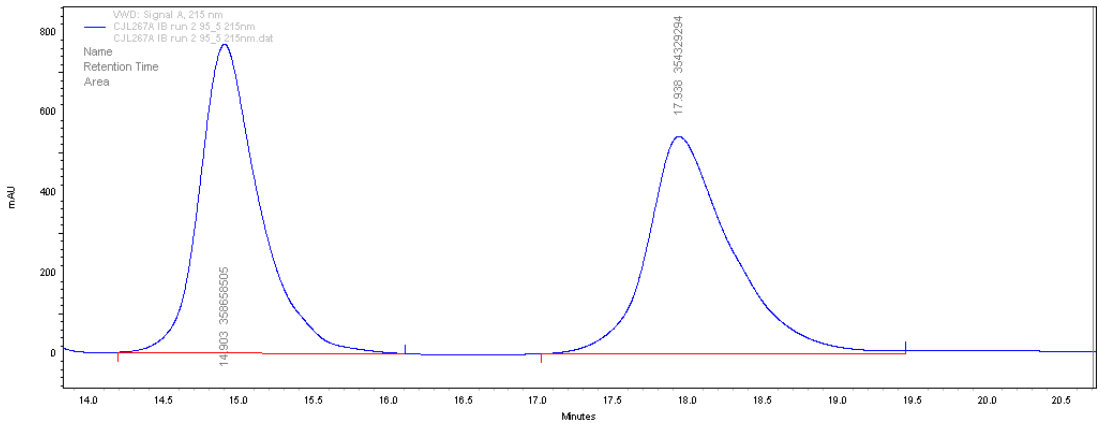
General enantioselective procedure A was followed, reacting *p*-methoxyphenyl boronic acid **3.2a** (36.5 mg, 0.24 mmol, 2.4 equiv.), Diels-Alder adduct **3.1f** (39.6 mg, 0.099 mmol, 1.0 equiv.), $Pd(OAc)_2$ (1.1 mg, 0.005 mmol, 0.01 equiv.) and ^{t}BuPyOx **3.5** (1.2 mg, 0.006 mmol, 0.012 equiv.) in DMF (1.0 mL) under an atmosphere of O_2 at 40 °C for 72 h. The resulting crude was purified by silica gel column chromatography (hexanes/EtOAc 10:1 → 7.5:1) to yield **3.3fa** (36.4 mg, 0.074 mmol, 72%, >20:1 d.r., 92:8 e.r.) as an off-white solid.

Mp: 145 °C (decomp.) (hexanes/chloroform); R_f: 0.2 in 7.5:1 petroleum ether:EtOAc; ν_{max}/ cm^{-1}: 2969, 1770, 1705, 1612,1513, 1487, 1252, 1180, 820, 732, 699; ^{1}H NMR (300 MHz, $CDCl_3$) 7.23 – 7.14 (m, 6H, Ar-H), 7.09 – 7.00 (m, 2H, Ar-H), 6.98 – 6.87 (m, 6H, Ar-H), 3.89 (dd, *J* = 9.9, 4.8 Hz, 1H, C<u>H</u>Ar), 3.81 (s, 3H, OCH_3), 3.57 (d, *J* = 10.6 Hz, 1H, CH), 3.50 (d, *J* = 10.6 Hz, 1H, CH), 3.23 (dd, *J* = 15.8, 9.9 Hz, 1H, C<u>H</u>H), 2.87 (dd, *J* = 15.8, 4.8 Hz, 1H), C<u>H</u>H, 2.09 (dt, *J* = 14.4, 7.4 Hz, 4H, C<u>HH</u>CH_3), 0.97 (t, *J* = 7.4 Hz, 3H, CH_3), 0.89 (t, *J* = 7.4 Hz, 3H, CH_3); δ ^{13}C NMR (75 MHz, $CDCl_3$) 206.41 (C), 206.36 (C), 199.8 (C), 159.3 (C), 143.7 (C), 143.3 (C), 134.1 (C), 134.0 (C), 129.3 (CH), 129.2 (CH), 128.8 (CH), 128.3 (CH), 128.2 (CH), 127.7 (CH), 127.6 (CH), 127.1 (C), 114.6 (C), 61.34 (C), 61.29 (C), 55.3 (CH_3), 52.5 (CH), 49.9 (CH), 49.1 (CH), 44.6 (CH_2), 19.2 (CH_3), 19.1 (CH_3), 9.4 (CH_3), 9.3 (CH_3); HRMS (TOF MS ASAP +) *m/z calc.* for $C_{34}H_{31}O_4$: 503.2222 $[M-H]^+$; found: 503.2218; $[\alpha]_D^{22.6}$ = + 46.5 (c 1.0 , $CHCl_3$); 92:8 e.r.; HPLC (CHIRALPAK IB, hexane/2-propanol: 95:5, flow rate: 1.0 mL min^{-1}, detection UV 215 nm, 25 °C) t_R of major isomer: 14.8 min, t_R of minor isomer: 18.1 min.

Enantioselective scale-up (1 mmol) procedure:

In a dry round bottom flask (25 mL), $Pd(OAc)_2$ (11.2 mg, 0.050 mmol, 0.05 equiv.) and ^{t}BuPyOx **3.5** (12.3 mg, 0.060 mmol, 0.06 equiv.) were pre-mixed in DMF (3 mL) for 15 minutes. Diels-Alder adduct **3.1f** (396.5 mg, 1.00 mmol, 1.0 equiv.) and *p*-methoxyphenyl boronic acid **3.2a** (364.8 mg, 2.40 mmol, 2.40 equiv.) were added, along with DMF (7 mL). The reaction mixture was stirred at 40 °C under an atmosphere of oxygen (balloon) for 72 h. The reaction was then diluted with 2:1 Et_2O:EtOAc (45 mL) and the organic layer was washed with H_2O (5 × 5 mL) and brine (1 × 10 mL), the combined organic layers were dried over $MgSO_4$ and solvent was removed under reduced pressure. The resulting crude was purified by silica gel column chromatography (gradient 20:1 hexanes:EtOAc + 10% toluene → 5:1 hexanes:EtOAc + 10% toluene) to yield **3.3fa** (304.6 mg, 603.6 mmol, 60%, >20:1 d.r., 93:7 e.r.) as a pale yellow fluffy solid.

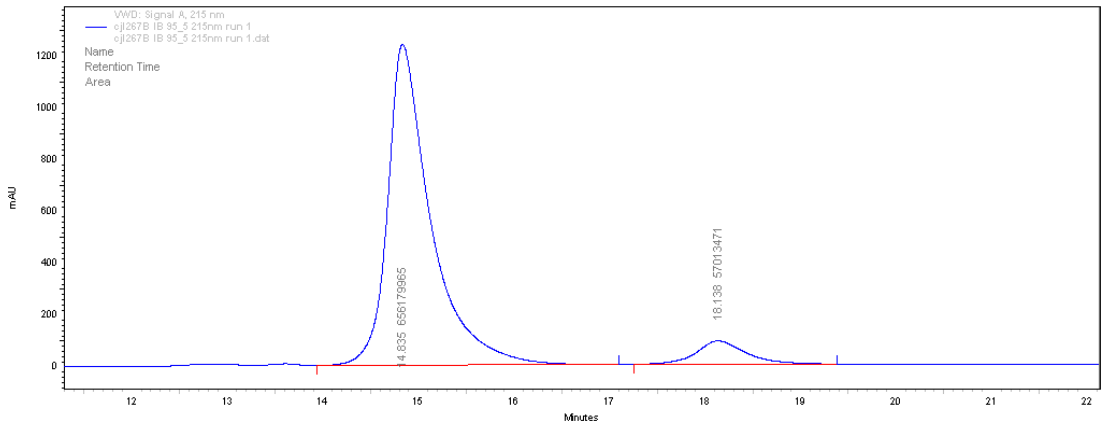
For characterisation, please see the enantioselective procedure above.



VWD: Signal A, 215 nm Results

Retention Time	Area	Area %	Height	Height %
14.903	358658505	50.30	12874685	58.66
17.938	354329294	49.70	9074554	41.34
Totals	712987799	100.00	21949239	100.00

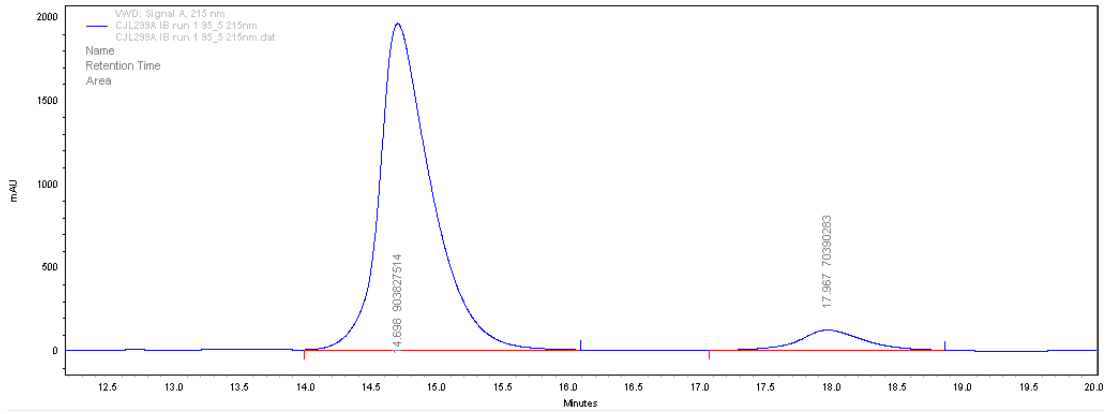
HPLC trace for 0.1 mmol scale:



VWD: Signal A, 215 nm Results

Retention Time	Area	Area %	Height	Height %
14.835	656179965	92.01	20826138	93.17
18.138	57013471	7.99	1527778	6.83
Totals	713193436	100.00	22353916	100.00

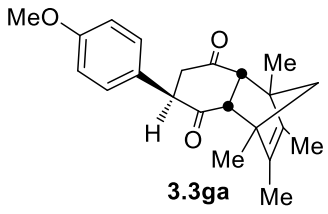
HPLC trace for 1.0 mmol scale:



VWD: Signal A, 215 nm Results

Retention Time	Area	Area %	Height	Height %
14.698	903827514	92.77	32776604	94.13
17.967	70390283	7.23	2045609	5.87
Totals	974217797	100.00	34822213	100.00

6-(4-Methoxyphenyl)-1,2,3,4-tetramethyl-1,4,4a,6,7,8a-hexahydro-1,4-methanonaphthalene-5,8-dione 3.3ga



3.3ga

Racemic procedure:

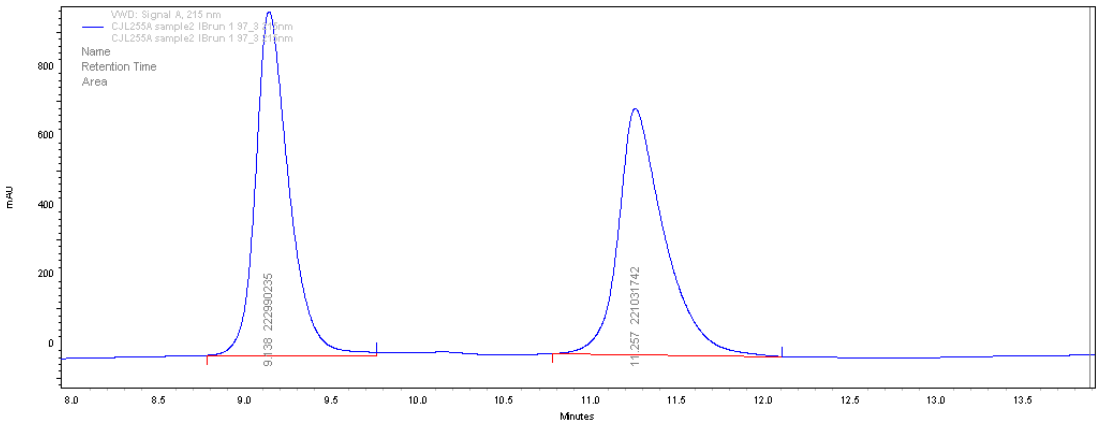
General racemic procedure was followed, reacting *p*-methoxyphenyl boronic acid **3.2a** (36.5 mg, 0.24 mmol, 2.4 equiv.), Diels-Alder adduct **3.1g** (23.0 mg, 0.099 mmol, 1.0 equiv.), $Pd(OAc)_2$ (1.1 mg, 0.005 mmol, 0.05 equiv.) and 1,10-phenanthroline **3.17** (1.1 mg, 0.006 mmol, 0.06 equiv.) in DMF (1.0 mL) under an atmosphere of O_2 (balloon) at 40 °C for 24 h. The resulting crude was purified by silica gel column chromatography (hexane:EtOAc 20:1 → 10:1) to yield **3.3ga** (25.1 mg, 0.077 mmol, 77%, >20:1 d.r.) as a white powder solid.

Enantioselective procedure:

General enantioselective procedure C was followed with modifications, reacting recrystallised *p*-methoxyphenyl boronic acid **3.2a** (30.6 mg, 0.20 mmol, 2.0 equiv.), Diels-Alder adduct **3.1g** (35.4 mg, 0.099 mmol, 1.0 equiv.), $Pd(OTFA)_2$ (1.7 mg, 0.005 mmol, 0.05 equiv.) and 5-CF_3-^{t}BuPyOx **3.6** (1.6 mg, 0.006 mmol, 0.06 equiv.) in DCE (0.5 mL) at 40 °C for 72 h. The resulting crude was purified by silica gel column chromatography (hexane:EtOAc 15:1 → 10:1) to yield **3.3ga** (22.3 mg, 0.068 mmol, 68%, >20:1 d.r., 95:5 e.r.) as a white powder.

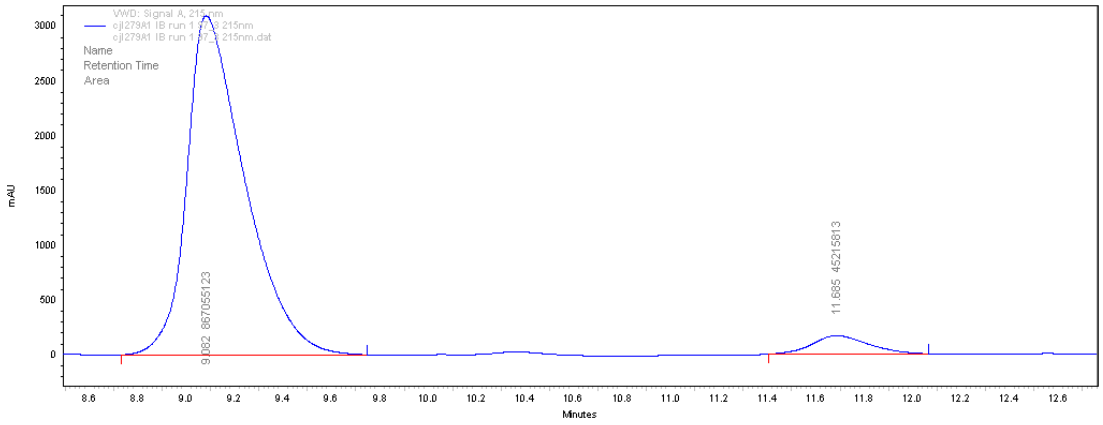
Mp: 123-125 °C (hexane/chloroform); R_f: 0.2 in 10:1 petroleum ether:EtOAc; ν_{max}/ cm^{-1}: 2926, 2859, 1702, 1609, 1512, 1445, 1249, 1181, 839; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.03 – 6.97 (m, 2H, Ar-H), 6.88 – 6.82 (m, 2H, Ar-H), 3.78 (s, 3H, OCH_3), 3.45 (dd, *J* = 9.7, 4.9 Hz, 1H, C<u>H</u>Ar), 2.97 (d, *J* = 9.4 Hz, 1H, CH), 2.93 (dd, *J* = 15.9, 9.7 Hz, 1H, C<u>H</u>H), 2.88 (d, *J* = 9.4 Hz, 1H, CH), 2.49 (dd, *J* = 15.9, 4.9 Hz, 1H, CH<u>H</u>), 1.62 (s,

3H, CH_3), 1.61 (s, 3H, CH_3), 1.48 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 1.22 (d, J = 8.3 Hz, 1H, C<u>H</u>H), 1.18 (d, J = 8.3 Hz, 1H, CH<u>H</u>); ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.3 (C), 208.9 (C), 159.0 (C), 138.9 (C), 138.6 (C), 129.0 (CH), 128.1 (C), 114.4 (CH), 62.7 (CH_2), 59.3 (CH), 58.3 (CH), 57.1 (C), 57.0 (C), 55.4 (CH_3), 52.0 (CH), 44.8 (CH_2), 17.2 (CH_3), 17.0 (CH_3), 11.7 (CH_3), 11.5 (CH_3); HRMS (TOF MS ASAP +) *m/z calc.* for $C_{22}H_{25}O_3$: 337.1804 $[M+H]^+$; found: 337.1805; $[\alpha]_D^{22.0}$ = +54.8 (c 1.0, $CHCl_3$); 95:5 e.r.; HPLC (CHIRALPAK IB, hexane/2-propanol: 97:3, flow rate: 1.0 mL min^{-1}, detection UV 215 nm, 25 °C) t_R of major isomer: 9.1 min, t_R of minor isomer: 11.7 min.



VWD: Signal A, 215 nm Results

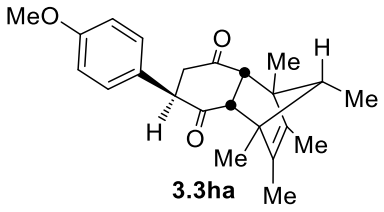
Retention Time	Area	Area %	Height	Height %
9.138	222990235	50.22	16660880	58.26
11.257	221031742	49.78	11936449	41.74
Totals	444021977	100.00	28597329	100.00



VWD: Signal A, 215 nm Results

Retention Time	Area	Area %	Height	Height %
9.082	867055123	95.04	51954124	94.88
11.685	45215813	4.96	2802255	5.12
Totals	912270936	100.00	54756379	100.00

6-(4-Methoxyphenyl)-1,2,3,4,9-pentamethyl-1,4,4a,6,7,8a-hexahydro-1,4-methanonaphthalene-5,8-dione 3.3ha



3.3ha

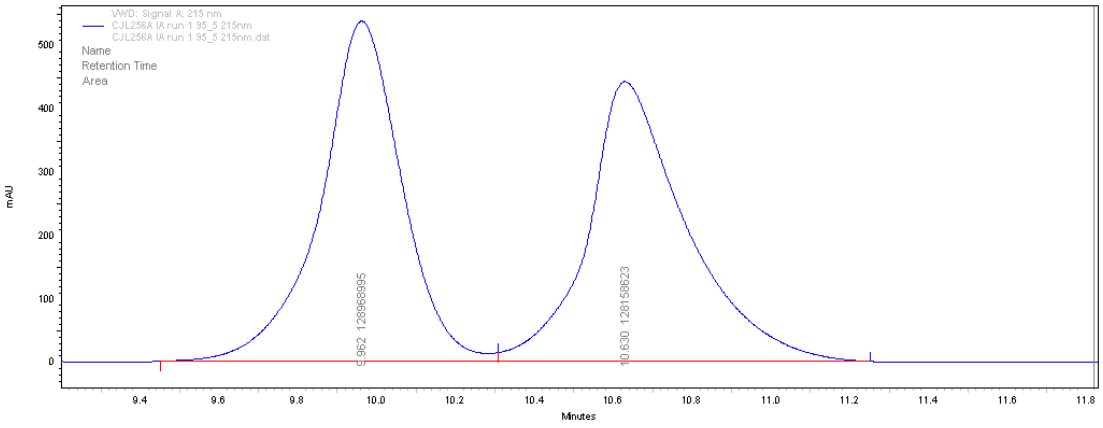
Racemic procedure:

General racemic procedure was followed with modifications and on a reduced scale, reacting *p*-methoxyphenyl boronic acid **3.2a** (18.2 mg, 0.12 mmol, 2.4 equiv.), Diels-Alder adduct **3.1h** (12.2mg, 0.050 mmol, 1.0 equiv., 20:1 d.r.), $Pd(OAc)_2$ (1.1, 0.005 mmol, 0.01 equiv.) and 1,10-phenanthroline **3.17** (1.1 mg, 0.006 mmol, 0.012 equiv.) in DMF (1.0 mL) under an atmosphere of O_2 at 40 °C for 24 h. The resulting crude was purified by silica gel column chromatography (hexane:EtOAc 20:1 → 10:1) to yield **3.3ha** (15.2 mg, 0.086 mmol, 86%, >20:1 d.r.) as a white crystalline powder.

Enantioselective procedure:

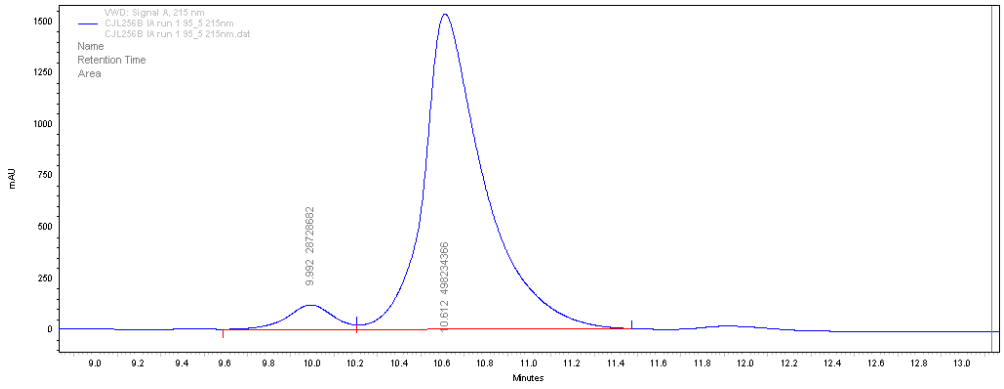
General enantioselective procedure C was followed, reacting recrystallised *p*-methoxyphenyl boronic acid **3.2a** (30.6 mg, 0.20 mmol, 2.0 equiv.), Diels-Alder adduct **3.1h** (24.4 mg, 0.099 mmol, 1.0 equiv.), $Pd(OTFA)_2$ (1.7 mg, 0.005 mmol, 0.05 equiv.) and 5-CF_3-^{t}BuPyOx **3.6** (1.6 mg, 0.006 mmol, 0.06 equiv.) in DCE (0.5 mL) at 40 °C for 72 h. The resulting crude was purified by silica gel column chromatography (hexane:EtOAc 15:1 → 10:1) to yield **3.3ha** (18.9 mg, 0.054 mmol, 64%, >20:1 d.r., 95:5 e.r.) as a white powder.

Mp: 126-129 °C (hexane/chloroform); R_f: 0.2 in 10:1 petroleum ether:EtOAc; ν_{max}/ cm^{-1}: 2956, 2928, 2868, 1702, 1699, 1652, 1512, 1445, 1250, 1182, 841, ; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.04 – 6.97 (m, 2H, Ar-H), 6.91 – 6.82 (m, 2H, Ar-H), 3.78 (s, 3H, OCH_3), 3.45 (dd, *J* = 9.9, 5.0 Hz, 1H, C<u>H</u>Ar), 2.91 (dd, *J* = 15.8, 9.9 Hz, 1H, C<u>H</u>H), 2.89 (d, *J* = 9.2 Hz, 1H, CH), 2.80 (d, *J* = 9.2 Hz, 1H, CH), 2.49 (dd, *J* = 15.8, 5.0 Hz, 1H, CH<u>H</u>), 1.58 (s, 3H, CH_3), 1.57 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 1.33 (d, *J* = 6.4 Hz, 2H, C<u>H</u>CH_3), 1.29 (s, 3H, CH_3), 0.56 (d, *J* = 6.4 Hz, 3H, CH<u>CH_3</u>); ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.4 (C), 209.0 (C), 159.0 (C), 135.3 (C), 134.9 (C), 129.0 (CH), 128.3 (C), 114.4 (CH), 63.3 (CH), 60.1 (C), 59.9 (C), 59.4 (CH), 58.4 (CH), 55.4 (CH_3), 52.2 (CH), 45.0 (CH_2), 14.8 (CH_3), 14.5 (CH_3), 12.1 (CH_3), 11.8 (CH_3), 7.4 (CH_3); δ HRMS (TOF MS ASAP +) *m/z calc.* for $C_{23}H_{27}O_3$: 351.1960 $[M+H]^+$; found: 351.1960; $[\alpha]_D^{20.6}$ = + 66.0 (c 1.18, $CHCl_3$); 95:5 e.r.; HPLC (CHIRALPAK IA, hexane/2-propanol: 95:5, flow rate: 1.0 mL min^{-1}, detection UV 215 nm, 25 °C) t_R of major isomer: 10.6 min, t_R of minor isomer: 10.0 min.



VWD: Signal A, 215 nm Results

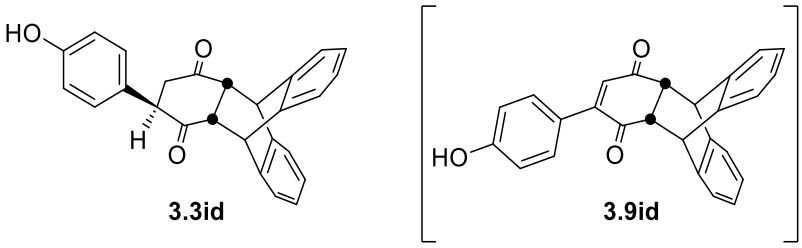
Retention Time	Area	Area %	Height	Height %
9.962	128968995	50.16	9013234	54.86
10.630	128158623	49.84	7415971	45.14
Totals	257127618	100.00	16429205	100.00



VWD: Signal A, 215 nm Results

Retention Time	Area	Area %	Height	Height %
9.992	28728682	5.45	1982855	7.16
10.612	498234366	94.55	25728465	92.84
Totals	526963048	100.00	27711320	100.00

14-(4-Methoxyphenyl)-9,10-dihydro-9,10-[1,2]benzenoanthracene-13,16-dione 3.3id



Racemic procedure:

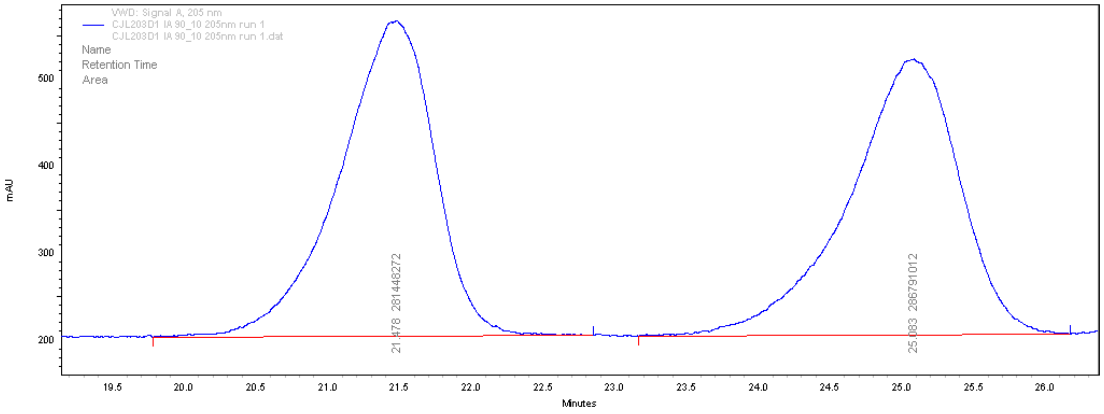
General racemic procedure was followed, reacting *p*-hydroxyphenyl boronic acid **3.2d** (33.1 mg, 0.24 mmol, 2.4 equiv.), Diels-Alder adduct **3.1i** (28.6 mg, 0.099 mmol, 1.0 equiv.), $Pd(OAc)_2$ (1.1 mg, 0.005 mmol, 0.01 equiv.) and 1,10-phenanthroline **3.17** (1.1 mg, 0.006 mmol, 0.012 equiv.) in DMF (1.0 mL) under an atmosphere of O_2 at 40 °C for 24 h. The resulting crude was purified by silica gel column chromatography (petroleum ether/EtOAc 3:1) to yield a 2:1 inseparable mixture of **3.3id:3.9id** (37.5 mg, 0.098 mmol, 98%) as a yellow oil. The oxidative Heck product **3.9id** was confirmed by comparison of the **3.3id/3.9id** mixture ^{1}H NMR spectra with pure ^{1}H NMR spectra of **3.3id**, remaining signals could be clearly assigned to **3.9id**.

Enantioselective procedure:

General enantioselective procedure C was followed with modifications, reacting *p*-hydroxyphenyl boronic acid **3.2d** (33.1mg, 0.24 mmol, 2.4 equiv.), Diels-Alder adduct **3.1i** (28.6 mg, 0.099 mmol, 1.0 equiv.), $Pd(OTFA)_2$ (1.7 mg, 0.005 mmol, 0.05 equiv.) and ^{t}BuPyOx **3.7** (1.2 mg, 0.006 mmol, 0.006 mmol, 0.06 equiv.) in DCE (0.5 mL) at 40 °C for 48 h. The resulting crude was purified by silica gel column chromatography (hexanes/EtOAc 5:1 → 3:1) to yield **3.3id** (24.7 mg, 0.065 mmol, 65%, >20:1 d.r., 85:15 e.r.) as an off-white powder.

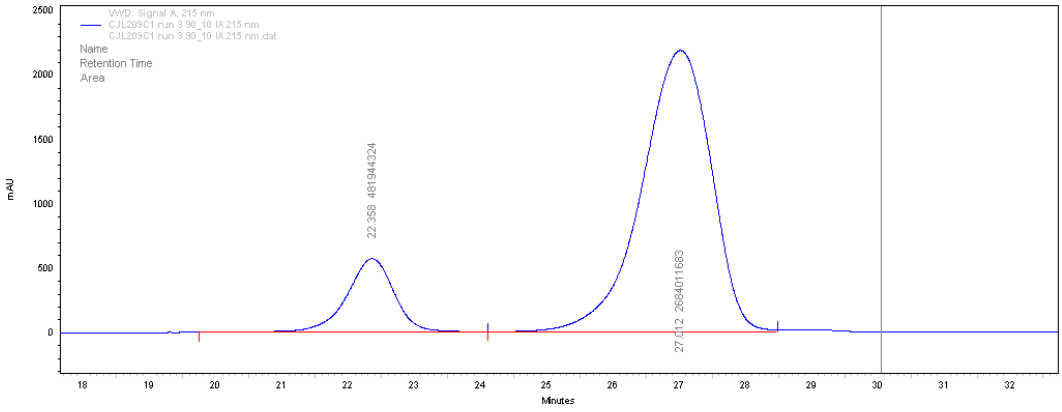
Mp: 107-109 °C (decomp.) (hexanes/chloroform); R_f: 0.2 in 3:1 petroleum ether:EtOAc; νmax/ cm^{-1}: 3465, 3013, 1698, 1614, 1595, 1516, 1204, 1148, 842, 774, 750; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (m, 2H, Ar-H), 7.33 – 7.28 (m, 2H, Ar-H),

7.19 – 7.15 (m, 2H, Ar-H), 7.14 (m, 2H, Ar-H), 6.80 (d, *J* = 8.6 Hz, 2H, Ar-H), 6.72 (d, *J* = 8.6 Hz, 2H, Ar-H), 4.94 (d, *J* = 2.7 Hz, 1H, CHAr), 4.90 (d, *J* = 2.7 Hz, 1H, CHAr), 4.89 (s, 1H, OH), 3.08 (dd, *J* = 10.6, 2.6 Hz, 1H, CH), 2.97 (dd, *J* = 10.6, 2.6, 1H, CH), 2.90 – 2.80 (m, 2H, CHH + CHAr), 1.98 – 1.88 (m, 1H, CHH); δ ^{13}C NMR (101 MHz, $CDCl_3$) 207.9 (C), 207.6 (C), 155.1 (C), 141.8 (C), 141.8 (C), 140.8 (C), 140.7 (C), 128.8 (CH), 127.4 (C), 126.7 (CH), 126.6 (CH), 126.5 (CH), 125.2 (CH), 125.1 CH), 123.8 (CH), 123.8 (CH), 115.8 (CH), 51.8 (CH), 51.2 (CH), 50.4 (CH), 47.9 (CH), 47.6 (CH), 43.0 (CH_2), 1 × overlapping CH signal; HRMS (TOF MS ASAP +) *m/z calc.* for $C_{26}H_{19}O_3$: 379.1334 $[M+H]^+$; found: 379.1333; $[\alpha]_D^{24.1}$ = + 16.4 (c 0.9, $CHCl_3$); 85:15 e.r.; HPLC (CHIRALPAK IA, hexane/2-propanol: 90:10, flow rate: 1.0 mL min^{-1}, detection UV 205 nm, 25 °C) t_R of major isomer: 27.012 min, t_R of minor isomer: 22.358 min.



VWD: Signal A, 205 nm Results

Retention Time	Area	Area %	Height	Height %
21.478	281448272	49.53	6091798	53.36
25.083	286791012	50.47	5325205	46.64
Totals	568239284	100.00	11417003	100.00

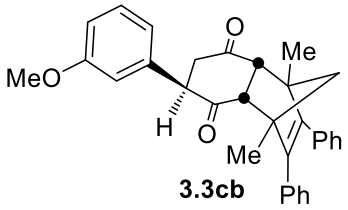


VWD: Signal A, 215 nm Results

Retention Time	Area	Area %	Height	Height %
22.358	481944324	15.22	9592696	20.71
27.012	2684011683	84.78	36722983	79.29
Totals	3165956007	100.00	46315679	100.00

3.9.5 Boronic Acid 3.2 Screen

6-(3-Methoxyphenyl)-1,4-dimethyl-2,3-diphenyl-1,4,4a,6,7,8a-hexahydro-1,4-methanonaphthalene-5,8-dione 3.3cb



3.3cb

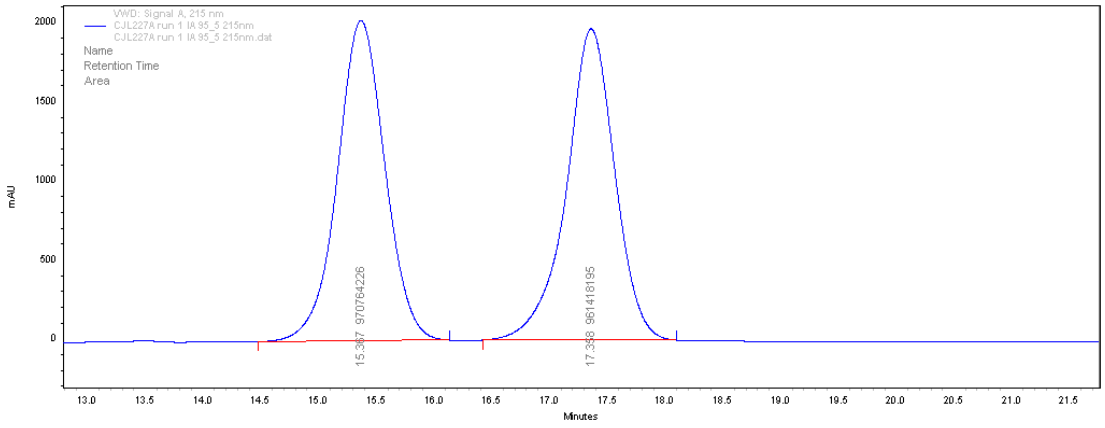
Racemic procedure:

General racemic procedure was followed, reacting *m*-methoxybenzene boronic acid **3.2b** (36.5 mg, 0.24 mmol, 2.4 equiv.) with Diels-Alder adduct **3.1c** (35.4 mg, 0.099 mmol, 1 equiv.), $Pd(OAc)_2$ (1.1 mg, 0.005 mmol, 0.05 equiv.) and 1,10-phenanthroline **3.17** (1.1 mg, 0.006 mmol, 0.06 equiv.) in DMF (1 mL) under an atmosphere of O_2 (balloon) at 40 °C for 24 h. The resulting crude was purified by silica gel column chromatography (toluene/EtOAc 20:1→10:1) to yield **3.3cb** (32.3 mg, 0.070 mmol, 70%, >20:1 d.r.) as a colourless fluffy solid.

Enantioselective procedure:

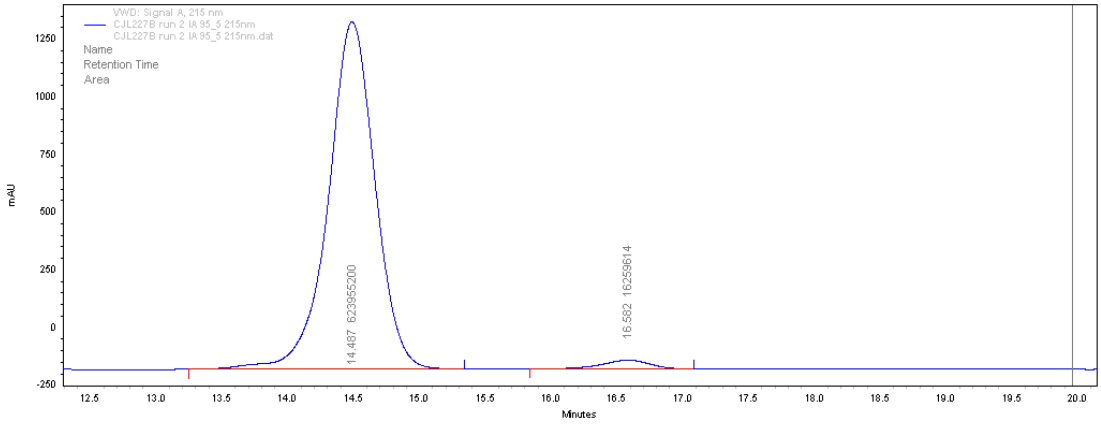
General enantioselective procedure A was followed, reacting *m*-methoxybenzene boronic acid **3.2b** (36.5 mg, 0.24 mmol, 2.4 equiv.) with Diels-Alder adduct **3.1c** (35.4 mg, 0.099 mmol, 1 equiv.), $Pd(OAc)_2$ (1.1 mg, 0.005 mmol, 0.05 equiv.) and ^{t}BuPyOx **3.5** (1.2 mg, 0.006 mmol, 0.06 equiv.) in DMF (1 mL) under an atmosphere of O_2 (balloon) at 40 °C for 24 h. The resulting crude was purified by silica gel column chromatography (petroleum ether/EtOAc 10:1 + 10% toluene) to yield **3.3cb** (27.0 mg, 0.058 mmol, 58%, >20:1 d.r., 97:3 e.r.) as a colourless fluffy solid.

Mp: 51-54 °C (petroleum ether/EtOAc); R_f: 0.2 in 10:1 petroleum ether:EtOAc; ν_{max}/ cm^{-1}: 2627, 2870, 1698, 1599, 1585, 1491, 1038, 741, 724, 697; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 – 7.22 (m, 1H, Ar-H), 7.22 – 7.13 (m, 6H, Ar-H), 6.98 – 6.87 (m, 4H, Ar-H), 6.87 – 6.80 (m, 1H, Ar-H), 6.71 – 6.65 (m, 1H, Ar-H), 6.65 – 6.60 (m, 1H, Ar-H), 3.90 (dd, *J* = 10.0, 5.2 Hz, 1H, C<u>H</u>Ar), 3.77 (s, 3H, OMe), 3.30 (d, *J* = 9.9 Hz, 1H, CH), 3.22 (d, *J* = 9.9 Hz, 1H, CH), 3.09 (dd, *J* = 16.0, 10.0 Hz, 1H, C<u>H</u>H), 2.82 (dd, *J* = 16.0, 5.2 Hz, 1H, CH<u>H</u>), 1.84 (d, *J* = 8.5 Hz, 1H, C<u>H</u>H), 1.62 (s, 3H, CH_3), 1.59 (d, *J* = 8.5 Hz, 1H, CH<u>H</u>), 1.56 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.4 (C), 208.3 (C), 160.0 (C), 147.3 (C), 146.8 (C), 137.7 (C), 135.6 (C), 135.4 (C), 130.0 (CH), 129.3 (CH), 129.2 (CH), 128.3 (CH), 128.1 (CH), 127.1 (CH), 120.2 (CH), 114.0 (CH), 113.2 (CH), 66.0 (CH_2), 60.1 (CH), 59.0 (CH), 58.1 (2 × C), 55.3 (CH_3), 52.9 (CH), 45.1 (CH_2), 19.1 (CH_3), 18.8 (CH_3) with 1 overlapping aromatic CH signal; δ HRMS (TOF MS ASAP+) *m/z calc.* for $C_{32}H_{29}O_3$: 461.2117 $[M-H]^+$; found: 461.2110; $[\alpha]_D^{19.1}$ = +20.3 (*c* 1.63, $CHCl_3$); 97:3 e.r.; HPLC (CHIRALPAK IA, hexane/2-propanol: 95:5, flow rate: 1.0 mL min^{-1}, detection UV 215 nm, 25 °C) t_R of major isomer: 14.487 min, t_R of minor isomer: 16.582 min.



VWD: Signal A,
215 nm Results

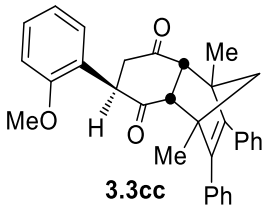
Retention Time	Area	Area %	Height	Height %
15.367	970764226	50.24	33936076	50.70
17.358	961418195	49.76	32995594	49.30
Totals	1932182421	100.00	66931670	100.00



VWD: Signal A,
215 nm Results

Retention Time	Area	Area %	Height	Height %
14.487	623955200	97.46	25252947	97.53
16.582	16259614	2.54	639770	2.47
Totals	640214814	100.00	25892717	100.00

6-(2-Methoxyphenyl)-1,4-dimethyl-2,3-diphenyl-1,4,4a,6,7,8a-hexahydro-1,4-methanonaphthalene-5,8-dione 3.3cc



3.3cc

Racemic procedure:

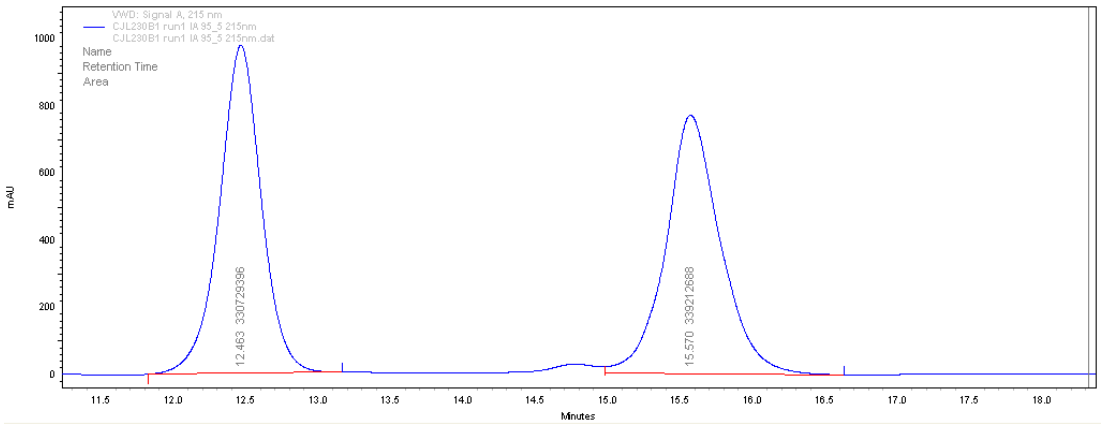
General racemic procedure was used with modifications, reacting *o*-methoxyphenyl boronic acid **3.2c** (36.4.0 mg, 0.24 mmol, 2.4 equiv.), Diels-Alder adduct **3.1c** (35.4 mg, 0.099 mmol, 1.0 equiv.), $Pd(OAc)_2$ (1.1 mg, 0.005 mmol, 0.05 equiv.) and 1,10-phenanthroline **3.17** (1.1 mg, 0.006 mmol, 0.06 equiv.) in DMF (1 mL) under an atmosphere of O_2 (balloon) at 50 °C for 24 h. The resulting crude was purified by silica gel column chromatography (petroleum ether/EtOAc 10:1 + 10% toluene) to yield **3.3cc** (23.1 mg, 0.05 mmol, 50%, >20:1 d.r.) as a white solid.

Enantioselective procedure:

General enantioselective procedure B was followed, reacting *o*-methoxyphenyl boronic acid **3.2c** (3.4.0 mg, 0.24 mmol, 2.4 equiv.), Diels-Alder adduct **3.1c** (35.4 mg, 0.099 mmol, 1.0 equiv.), $Pd(OAc)_2$ (2.2 mg, 0.010 mmol, 0.10 equiv.) and ^{t}BuPyOx **3.5** (2.1 mg, 0.011 mmol, 0.11 equiv.) in DMF (1 mL) under an atmosphere of O_2 (balloon) at 40 °C for 72 h. The resulting crude was purified by silica gel column chromatography (petroleum ether/EtOAc 10:1 + 10% toluene) to yield **3.3cc** (21.1 mg, 0.046 mmol, 46%, >20:1 d.r., 92:8 e.r.) as a white powder.

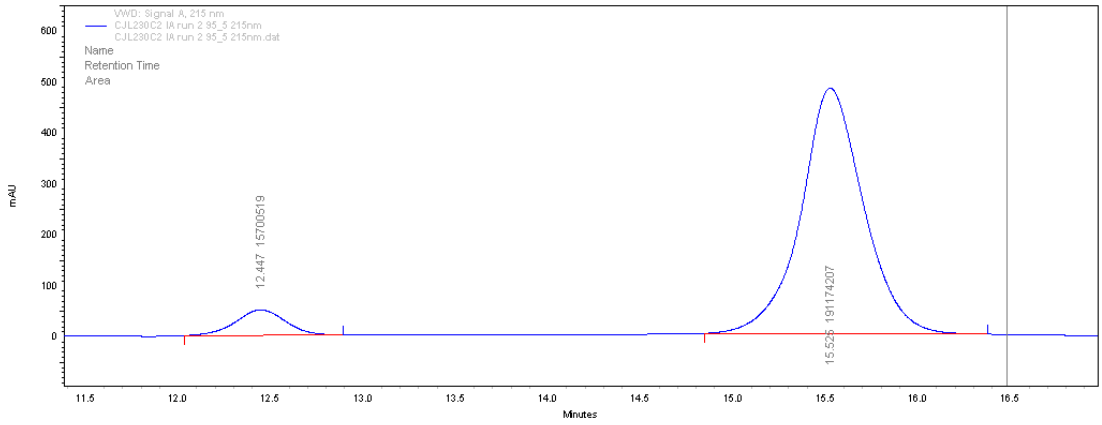
Mp: 135-137 °C; R_f: 0.2 in 10:1 petroleum ether:EtOAc; ν_{max}/ cm^{-1}: 2924, 1699, 1600, 1494, 1462, 1440, 1246, 1030, 752, 743, 698; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 – 7.17 (m, 4H, Ar-H), 7.13 – 7.03 (m, 5H, Ar-H), 7.00 (dd, *J* = 7.5, 1.8 Hz, 1H, Ar-H), 6.92 (td, *J* = 7.4, 1.1 Hz, 1H, Ar-H), 6.88 – 6.81 (m, 3H, Ar-H), 4.14 (dd, *J* = 11.8, 6.0 Hz, 1H, C<u>H</u>H), 3.57 (s, 3H, OCH_3), 3.40 (d, *J* = 9.9 Hz, 1H, CH), 3.27 (d, *J* = 9.9, 1H,

CH), 3.06 (dd, *J* = 16.1, 11.8 Hz, 1H), 2.72 (dd, *J* = 16.1, 6.0 Hz, 1H), 1.86 (d, *J* = 8.4 Hz, 1H, CH<u>H</u>), 1.68 (s, 3H, CH_3), 1.64 (d, *J* = 8.4 Hz, 1H, CH<u>H</u>), 1.49 (s, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.0 (C), 207.7 (C), 156.7 (C), 147.5 (C), 146.5 (C), 136.0 (C), 135.3 (C), 130.2 (C), 129.5 (CH), 129.2 (CH), 129.0 (CH), 128.2 (CH), 128.0 (CH), 127.0 (CH), 126.8 (CH), 126.4 (C), 121.0 (CH), 111.0 (CH), 66.2 (CH_2), 60.7 (CH), 60.1 (CH), 58.7 (C), 57.7 (C), 55.0 (CH_3), 48.6 (CH), 46.0 (CH_2), 19.4 (CH_3), 18.4 (CH_3); δ HRMS (FTMS + p NSI) *m/z calc.* for $C_{32}H_{30}O_3NH_4$: 480.2533 [M+NH_4^+]+; found: 480.2528; $[\alpha]_D^{21.0}$ = -12.0 (c 0.5, $CHCl_3$); 92:8 e.r.; HPLC (CHIRALPAK IA, hexane/2-propanol: 95:5, flow rate: 1.0 mL min^{-1}, detection UV 215 nm, 25 °C) t_R of major isomer: 15.148 min, t_R of minor isomer: 12.303 min.



VWD: Signal A, 215 nm Results

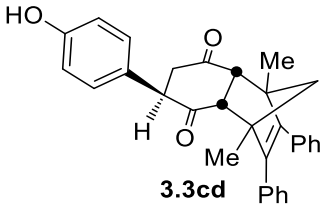
Retention Time	Area	Area %	Height	Height %
12.463	330729396	49.37	16420198	55.92
15.570	339212688	50.63	12943778	44.08
Totals	669942084	100.00	29363976	100.00



VWD: Signal A, 215 nm Results

Retention Time	Area	Area %	Height	Height %
12.447	15700519	7.59	837338	9.38
15.525	191174207	92.41	8091628	90.62
Totals	206874726	100.00	8928966	100.00

6-(4-Hydroxyphenyl)-1,4-dimethyl-2,3-diphenyl-1,4,4a,6,7,8a-hexahydro-1,4-methanonaphthalene-5,8-dione 3.3cd



3.3cd

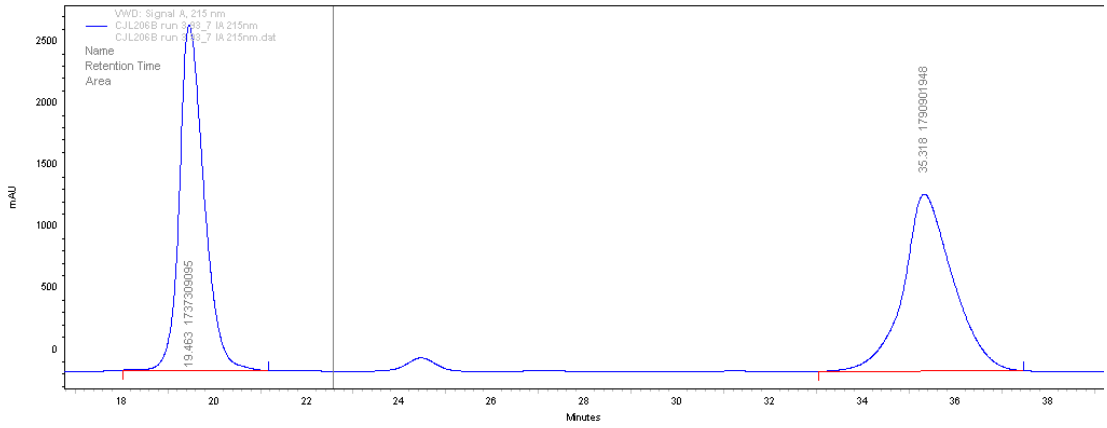
Racemic procedure:

General racemic procedure was followed, reacting p-hydroxyphenyl boronic acid **3.2d** (33.1 mg, 0.24 mmol, 2.4 equiv.), Diels-Alder adduct **3.1c** (35.4 mg, 0.099 mmol, 1 equiv.), $Pd(OAc)_2$ (1.1 mg, 0.005 mmol, 0.05 equiv.) and 1,10-phenanthroline **3.17** (1.1 mg, 0.006 mmol, 0.06 equiv.) in DMF (1 mL) under an atmosphere of O_2 (balloon) at 40 °C for 24 h. The resulting crude was purified by silica gel column chromatography (petroleum ether /EtOAc 10:1 → 3:1) to yield **3.3cd** (33.7 mg, 0.075 mmol, 75%, >20:1 d.r.) as a colourless oil.

Enantioselective procedure:

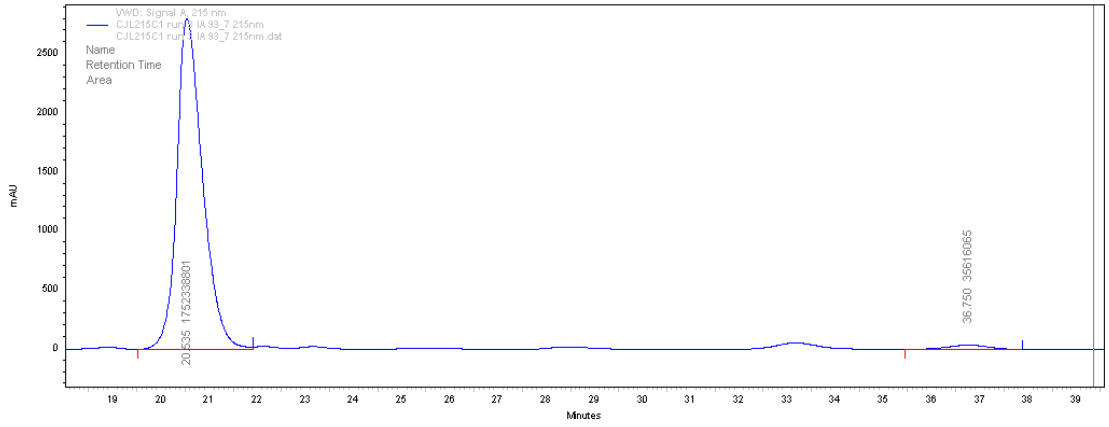
General enantioselective procedure A was followed, reacting *p*-hydroxyphenyl boronic acid **3.2d** (33.1 mg, 0.24 mmol, 2.4 equiv.), Diels-Alder adduct **3.1c** (35.4 mg, 0.099 mmol, 1 equiv.) $Pd(OAc)_2$ (1.1 mg, 0.005 mmol, 0.05 equiv.) and ^{t}BuPyOx **3.5** (1.2 mg, 0.006 mmol, 0.06 equiv.) in DMF (1 mL) under an atmosphere of O_2 (balloon) at 40 °C for 72 h. The resulting crude was purified by silica gel column chromatography (petroleum ether/EtOAc 10:1 → 3:1) to yield **3.3cd** (29.1 mg, 0.065 mmol, 65%, >20:1 d.r., 98:2 e.r.) as a colourless oil.

R_f: 0.3 in 3:1 petroleum ether:EtOAc; ν_{max}/ cm^{-1}: 3366, 2972, 2870, 1694, 1614, 1597, 1515, 822, 775, 698); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 – 7.11 (m, 6H, Ar-H), 6.96 – 6.85 (m, 6H, Ar-H), 6.77 – 6.70 (m, 2H, Ar-H), 5.87 (s, 1H, OH), 3.88 (dd, *J* = 9.6, 5.2 Hz, 1H, C<u>H</u>Ar), 3.29 (d, *J* = 9.9 Hz, 1H, CH), 3.21 (d, *J* = 9.9 Hz, 1H, CH), 3.08 (dd, *J* = 16.0, 9.6 Hz, 1H, C<u>H</u>H), 2.83 (dd, *J* = 16.0, 5.2 Hz, 1H, CH<u>H</u>), 1.84 (d, *J* = 8.5 Hz, 1H, C<u>H</u>H), 1.61 (s, 3H, CH_3), 1.57 (s, 4H, CH_3 and an overlapping CH<u>H</u> signal); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.7 (C), 209.2 (C), 155.5 (C), 147.1 (C), 146.9 (C), 135.5 (C), 135.4 (C), 129.3 (CH), 129.3 (CH), 129.2 (CH), 128.3 (CH), 128.2 (CH), 127.8 (C), 127.1 (CH), 116.0 (CH), 66.1 (CH_2), 60.2 (CH), 59.0 (CH), 58.2 (C), 58.1 (C), 52.2 (CH), 45.2 (CH_2), 19.0 (CH_3), 18.8 (CH_3), with 1 overlapping aromatic CH signals; HRMS (FTMS + p APCI corona) *m/z calc.* for $C_{31}H_{27}O_3$: 447.1955 $[M-H]^+$; found: 477.1945; $[\alpha]_D^{23.5}$ = +3.6 (*c* 0.3, $CHCl_3$); 98:2 e.r.; HPLC (CHIRALPAK IA, hexane/2-propanol: 97:3, flow rate: 1.0 mL min^{-1}, detection UV 215 nm, 25 °C) t_R of major isomer: 20.535 min, t_R of minor isomer: 36.750 min.



VWD: Signal A, 215 nm Results

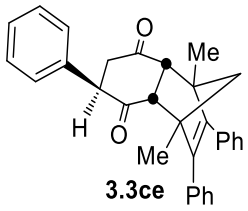
Retention Time	Area	Area %	Height	Height %
19.463	1737309095	49.24	46980970	66.11
35.318	1790901948	50.76	24087665	33.89
Totals	3528211043	100.00	71068635	100.00



VWD: Signal A, 215 nm Results

Retention Time	Area	Area %	Height	Height %
20.535	1752338801	98.01	47104916	98.71
36.750	35616065	1.99	614149	1.29
Totals	1787954866	100.00	47719065	100.00

1,4-Dimethyl-2,3,6-triphenyl-1,4,4a,6,7,8a-hexahydro-1,4-methanonaphthalene-5,8-dione 3.3ce



3.3ce

Racemic procedure:

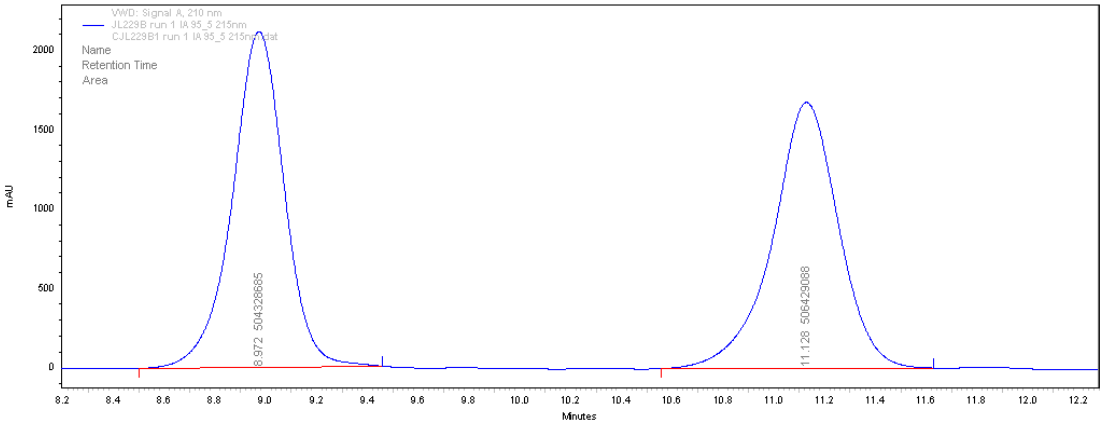
General racemic procedure was followed with modifications, reacting phenylboronic acid **3.2e** (29.3 mg, 0.24 mmol, 2.4 equiv.) with Diels-Alder adduct **3.1c** (35.4 mg, 0.099 mmol, 1.0 equiv.), $Pd(OAc)_2$ (1.1 mg, 0.005 mmol, 0.05 equiv.) and 1,10-phenanthroline (1.1 mg, 0.006 mmol, 0.06 equiv.) in DMF (0.5 mL) under an atmosphere of O_2 (balloon) at 40 °C for 24 h. The resulting crude was purified by silica gel column chromatography (toluene/EtOAc 10:1 + 10% toluene) to yield **3.3ce** (29.9 mg, 0.069 mmol, 69%, >20:1 d.r.) as a fluffy white solid.

Enantioselective procedure:

General enantioselective procedure B was followed, reacting phenylboronic acid **3.2e** (29.3 mg, 0.24 mmol, 2.4 equiv.), Diels-Alder adduct **3.1c** (35.4 mg, 0.099 mmol, 1.0 equiv.), $Pd(OAc)_2$ (2.2 mg, 0.010 mmol, 0.10 equiv.) and ^{t}BuPyOx **3.5** (2.1 mg, 0.011 mmol, 0.11 equiv.) in DMF (0.5 mL) under an atmosphere of O_2 (balloon) at 40 °C for 72 h.. The resulting crude was purified by silica gel column chromatography (petroleum ether/EtOAc 10:1 + 10% toluene) to yield **3.3ce** (36.2 mg, 0.083 mmol, 83%, >20:1 d.r., 97:3 e.r.) as a white fluffy crystalline solid.

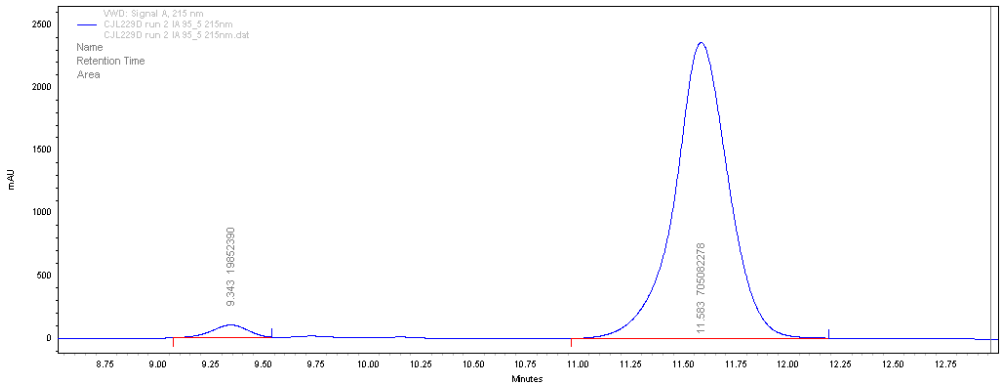
Mp: 56-58 °C; R_f: 0.2 in 10:1 petroleum ether:EtOAc; ν_{max}/ cm^{-1}: 3025, 2933, 2867, 1700, 100, 1574, 1454, 1041, 800, 775, 693; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 – 7.28 (m, 3H, Ar-H), 7.24 – 7.12 (m, 6H, Ar-H), 7.11 – 7.04 (m, 2H, Ar-H), 6.98 – 6.85 (m, 4H, Ar-H), 3.94 (dd, *J* = 10.4, 5.1 Hz, 1H, C<u>H</u>Ar), 3.30 (d, *J* = 9.9 Hz, 1H, CH), 3.22 (d, *J* = 9.9 Hz, 1H, CH), 3.10 (dd, *J* = 16.0, 10.4, 1H, C<u>H</u>H), 2.82 (dd, *J* = 16.0, 5.1 Hz,

1H, CHH), 1.84 (d, *J* = 8.5 Hz, 1H, CHH), 1.63 (s, 3H, CH_3), 1.59 (d, *J* = 8.5 Hz, 1H, CHH), 1.55 (s, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.4 (broad, C), 147.4 (C), 146.9 (C), 136.3 (broad, C), 135.7 (C), 135.5 (C), 129.4 (CH), 129.3 (CH), 129.0 (CH), 128.3 (CH), 128.2 (CH), 128.1 (CH), 127.8 (CH), 127.1 (CH), 66.2 (CH_2), 60.3 (CH), 59.2 (CH), 58.2 (C), 58.1 (C), 52.9 (CH), 45.3 (CH_2), 19.1 (CH_3), 18.7 (CH_3), 1 × overlapping C signals 1 × overlapping CH signal; HRMS (TOF MS ASAP +) *m/z calc.* for $C_{31}H_{29}O_2$: 433.2168 $[M+H]^+$; found: 433.2164; $[\alpha]_D^{20.4}$ = +10.1 (*c* 1.6, $CHCl_3$); 97:3 e.r.; HPLC (CHIRALPAK IA, hexane/2-propanol: 95:5, flow rate: 1.0 mL min^{-1}, detection UV 215 nm, 25 °C) t_R of major isomer: 11.583 min, t_R of minor isomer: 9.343 min.



VWD: Signal A, 210 nm Results

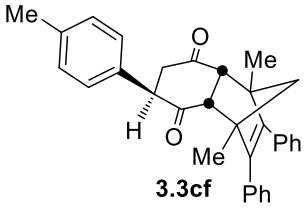
Retention Time	Area	Area %	Height	Height %
8.972	504328685	49.90	35478001	55.79
11.128	506429088	50.10	28117298	44.21
Totals	1010757773	100.00	63595299	100.00



VWD: Signal A, 215 nm Results

Retention Time	Area	Area %	Height	Height %
9.343	19852390	2.74	1661757	4.03
11.583	705082278	97.26	39578362	95.97
Totals	724934668	100.00	41240119	100.00

1,4-Dimethyl-2,3-diphenyl-6-(p-tolyl)-1,4,4a,6,7,8a-hexahydro-1,4-methanonaphthalene-5,8-dione 3.3cf



3.3cf

Racemic procedure:

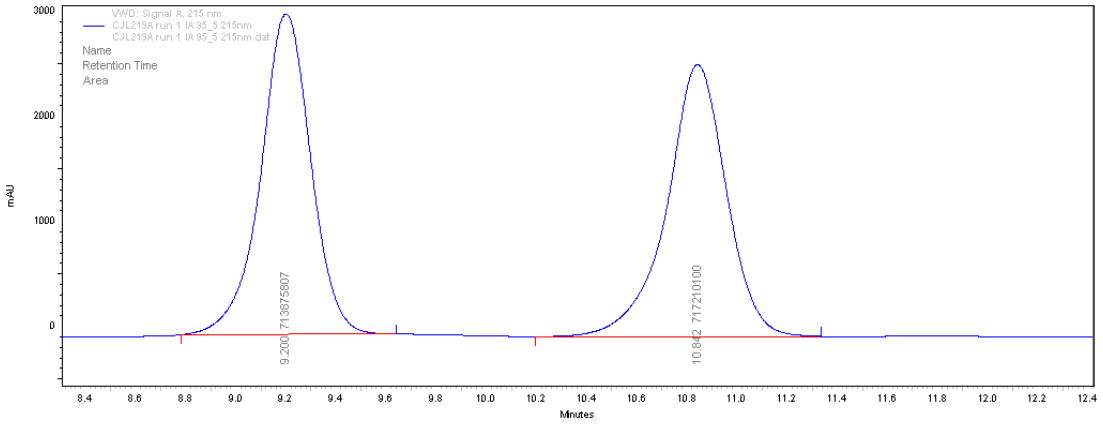
General racemic procedure was followed, reacting *p*-tolylphenyl boronic acid **3.2f** (32.6 mg, 0.24 mmol, 2.4 equiv.), Diels-Alder adduct **3.1c** (35.4 mg, 0.099 mmol, 1 equiv.), $Pd(OAc)_2$ (1.1 mg, 0.005 mmol, 0.05 equiv.) and 1,10-phenanthroline **3.17** (1.1 mg, 0.006 mmol, 0.06 equiv.) in DMF (1 mL) under an atmosphere of oxygen (balloon) at 40 °C for 24 h.. The resulting crude was purified by silica gel column chromatography (toluene/EtOAc 20:1→10:1) to yield **3.3cf** (40.3 mg, coeluted with starting material **43.1c**, >20:1 d.r.) as a pale-yellow oil.

Enantioselective procedure:

General enantioselective procedure B was followed, reacting *p*-tolylphenyl boronic acid **3.2f** (32.6 mg, 0.24 mmol, 2.4 equiv.) with Diels-Alder adduct **3.1c** (35.4 mg, 0.099

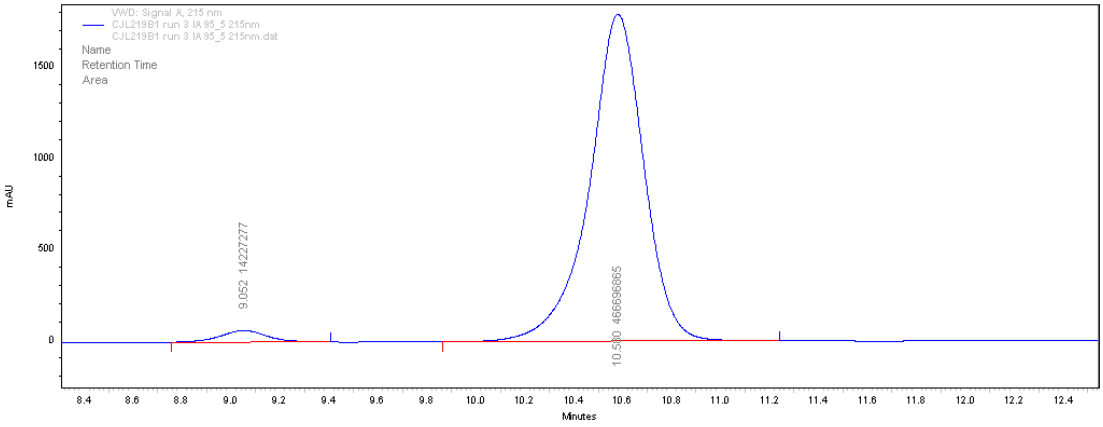
mmol, 1 equiv.), $Pd(OAc)_2$ (2.2 mg, 0.010 mmol, 0.10 equiv.) and ^{t}BuPyOx **3.5** (2.1 mg, 0.010 mmol, 0.10 equiv.) in DMF (1 mL) under an atmosphere of O_2 (balloon) at 40 °C for 72 h.. The resulting crude was purified by silica gel column chromatography (petroleum ether/EtOAc 10:1 → 3:1) to yield **3.3cf** (36.0 mg, 0.080 mmol, 81%, >20:1 d.r., 97:3 e.r.) as a colourless oil.

R_f: 0.2 in 10:1 petroleum ether:EtOAc; ν_{max}/ cm^{-1}: 2925, 2869,1699, 1599, 1574, 1488, 1442, 817, 743, 698;^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 – 7.12 (m, 8H, Ar-H), 7.02 – 6.86 (m, 6H, Ar-H), 3.91 (dd, *J* = 10.3, 5.1 Hz, 1H, C<u>H</u>Ar), 3.30 (d, *J* = 9.8 Hz, 1H, CH), 3.21 (d, *J* = 9.9 Hz, 1H, CH), 3.09 (dd, *J* = 16.0, 10.3 Hz, 1H, C<u>H</u>H), 2.81 (dd, *J* = 16.0, 5.1 Hz, 1H, CH<u>H</u>), 2.34 (s, 3H, CH_3), 1.84 (d, *J* = 8.5 Hz, 1H, C<u>H</u>H), 1.63 (s, 3H, CH_3), 1.59 (d, *J* = 8.5 Hz, 1H, CH<u>H</u>), 1.55 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.7 (C), 208.6 (C), 147.3, (C), 146.8 (C), 137.5(C), 135.6 (C), 135.4 (C), 133.1 (C), 129.7 (CH), 129.3 (CH), 129.2 (CH), 128.2 (CH), 128.1 (CH), 128.0 (CH), 127.03 (CH), 127.01 (CH), 66.1 (CH_2), 60.2 (CH), 59.0 (CH), 58.1 (C), 58.0 (C), 52.5 (CH), 45.3 (CH_2), 21.2 (CH_3), 19.1 (CH_3), 18.7 (CH_3); HRMS (+ p EI) *m/z calc.* for $C_{32}H_{30}O_2$: 446.2240 $[M]^+$; found: 446.2235; $[\alpha]_D^{22.1}$= +30.0 (*c* 1.0, $CHCl_3$); 97:3 e.r.; HPLC (CHIRALPAK IA, hexane/2-propanol: 95:5, flow rate: 1.0 mL min-1, detection UV 215 nm, 25 °C) t_R of major isomer: 10.580 min, t_R of minor isomer: 9.052 min.



VWD: Signal A, 215 nm Results

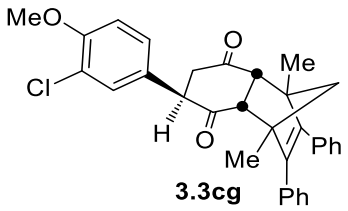
Retention Time	Area	Area %	Height	Height %
9.200	713875807	49.88	51203520	54.12
10.842	717210100	50.12	43411752	45.88
Totals	1431085907	100.00	94615272	100.00



VWD: Signal A, 215 nm Results

Retention Time	Area	Area %	Height	Height %
9.052	14227277	2.96	1069047	3.43
10.580	466696865	97.04	30122772	96.57
Totals	480924142	100.00	31191819	100.00

6-(4-Chloro-3-methoxyphenyl)-1,4-dimethyl-2,3-diphenyl-1,4,4a,6,7,8a-hexahydro-1,4-methanonaphthalene-5,8-dione 3.3cg



3.3cg

Racemic procedure:

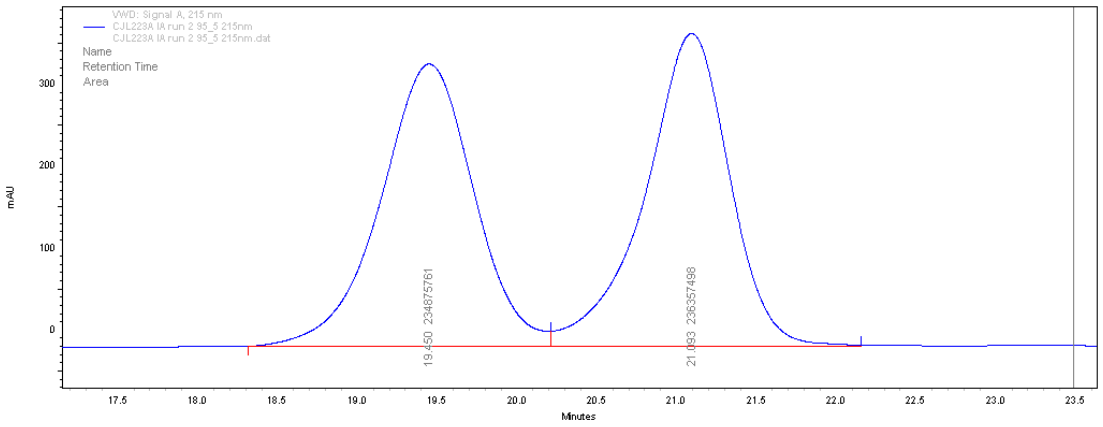
General racemic procedure was followed, eacting (4-chloro-3-methoxyphenyl)boronic acid **3.2g** (44.7 mg, 0.24 mmol, 2.4 equiv.), Diels-Alder adduct **3.1c** (35.4 mg, 0.099 mmol, 1 equiv.), $Pd(OAc)_2$ (1.1 mg, 0.005 mmol, 0.05 equiv.) and 1,10-phenanthroline **3.17** (1.1 mg, 0.006 mmol, 0.06 equiv.) in DMF (1 mL) under an atmosphere of O_2 (balloon) at 40 °C for 24 h.. The resulting crude was purified by silica gel column chromatography (petroleum ether/EtOAc 5:1 with 10% toluene) to yield **3.3cg** (28.6 mg, 0.058 mmol, 58%, >20:1 d.r.) as a colourless oil.

Enantioselective procedure:

General enantioselective procedure B was followed with modifications. (4-Chloro-3-methoxyphenyl)boronic acid **3.2g** (44.7 mg, 0.24 mmol, 2.4 equiv.) was dehydrated under vacuum with a heat gun in the reaction flask to the corresponding boroxine and reacted with Diels-Alder adduct **3.1c** (35.4 mg, 0.099 mmol, 1 equiv.), $Pd(OAc)_2$ (2.2 mg, 0.010 mmol, 0.10 equiv.) and ^{t}BuPyOx **3.5** (2.2 mg, 0.011 mmol, 0.11 equiv.) in DMF (1 mL) under an atmosphere of O_2 (balloon) at 40 °C for 24 h. Catalyst and ligand were not premixed. The resulting crude was purified by silica gel column chromatography (5:1 hexane:EtOAc with 10% toluene) to yield **3.3cg** (25.5 mg, 0.051 mmol, 51%, >20:1 d.r., 97:3 e.r.) as a colourless oil.

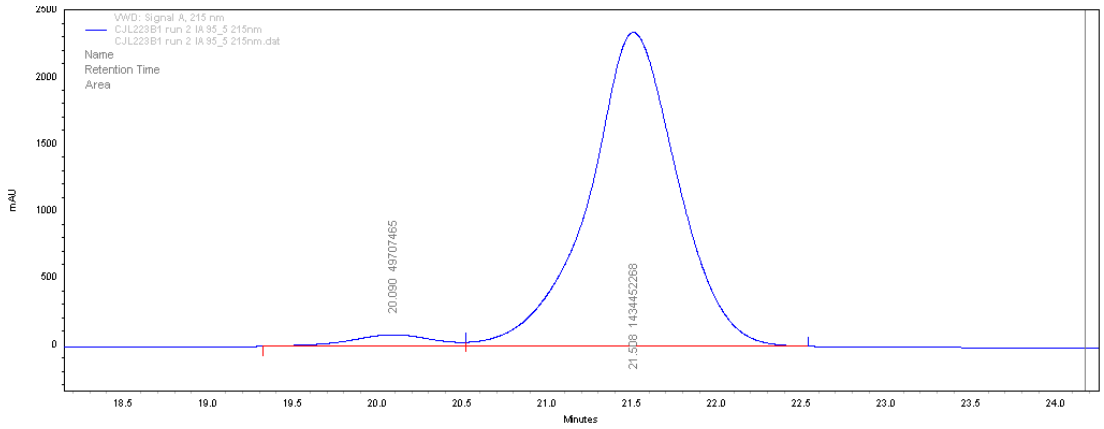
R_f: 0.2 in 5:1 petroleum ether:EtOAc; ν_{max}/ cm^{-1}: 2959, 2626, 2856, 1699, 1611, 1575, 1443,1274, 1105, 770, 727, 698, ;^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 – 7.12 (m, 6H, Ar-H), 7.08 – 7.05 (m, 1H, Ar-H), 6.98 – 6.83 (m, 6H, Ar-H), 3.89 (s, 3H, OMe), 3.85

(dd, *J* = 11.5, 5.0 Hz, 1H, C<u>H</u>Ar), 3.32 (d, *J* = 9.9 Hz, 1H, CH), 3.22 (d, *J* = 9.9 Hz, 1H, CH), 3.03 (dd, *J* = 15.9, 11.5 Hz, 1H, C<u>H</u>H), 2.78 (dd, *J* = 15.9, 5.0 Hz, 1H, CH<u>H</u>), 1.85 (d, *J* = 8.5 Hz, 1H, C<u>H</u>H), 1.64 (s, 3H, CH_3), 1.61 (d, *J* = 8.6 Hz, 1H, CH<u>H</u>), 1.52 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.5 (C), 207.7 (C), 154.6 (C), 147.6(C), 146.4 (C), 135.6 (C), 135.2 (C), 130.1 (CH), 129.2 (CH), 129.2 (CH), 129.1 (C), 128.3 (CH), 128.2 (CH), 127.4 (CH), 127.18 (CH) 127.16 (CH), 123.0 (C), 112.4 (CH), 66.1 (CH_2), 60.4 (CH), 59.2 (CH), 58.4 (C), 58.1 (C), 56.3 (CH_3), 51.4 (CH), 45.6 (CH_2), 19.2 (CH_3), 18.5 (CH_3); HRMS (TOF MS ASAP+) *m/z calc.* for $C_{32}H_{29}O_3Cl$: 496.1805 $[M+H]^+$; found: 496.1801; $[\alpha]_D^{22.1}$ = +24.0 (*c* 0.67, $CHCl_3$); 97:3 e.r.; HPLC (CHIRALPAK IA, hexane/2-propanol: 95:5, flow rate: 1.0 mL min^{-1}, detection UV 215 nm, 25 °C) t_R of major isomer: 21.508 min, t_R of minor isomer: 20.090 min.



VWD: Signal A, 215 nm Results

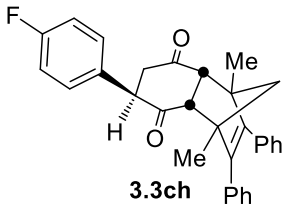
Retention Time	Area	Area %	Height	Height %
19.450	234875761	49.84	5781761	47.44
21.093	236357498	50.16	6406758	52.56
Totals	471233259	100.00	12188519	100.00



VWD: Signal A, 215 nm Results

Retention Time	Area	Area %	Height	Height %
20.090	49707465	3.35	1461615	3.58
21.508	1434452268	96.65	39358109	96.42
Totals	1484159733	100.00	40819724	100.00

6-(4-Fluorophenyl)-1,4-dimethyl-2,3-diphenyl-1,4,4a,6,7,8a-hexahydro-1,4-methanonaphthalene-5,8-dione 3.3ch



3.3ch

Racemic procedure:

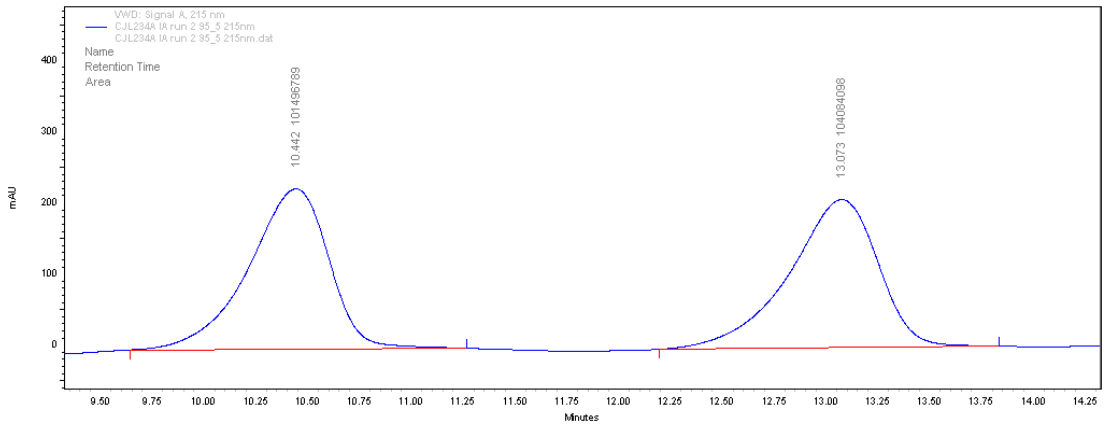
General racemic procedure was followed, reacting *p*-fluorobenzene boronic acid **3.2h** (33.6 mg, 0.24 mmol, 2.4 equiv.) with Diels-Alder adduct **3.1c** (35.4 mg, 0.099 mmol, 1.0 equiv.), $Pd(OAc)_2$ (1.1 mg, 0.005 mmol, 0.05 equiv.) and 1,10-phenanthroline **3.17** (1.1 mg, 0.006 mmol, 0.06 equiv.) in DMF (1 mL) under an atmosphere of O_2 (balloon) at 40 °C for 24 h. The resulting crude was purified by silica gel column chromatography (petroleum ether/EtOAc 10:1) to yield **3.3ch** (36.0 mg as a mixture of product and starting material **3.1c**, >20:1 d.r.) as a colourless oil.

Enantioselective procedure:

General enantioselective procedure B was followed. Reacting *p*-fluorobenzene boronic acid **3.2h** (33.6 mg, 0.24 mmol, 2.4 equiv.), Diels-Alder adduct **3.1c** (35.4 mg, 0.099 mmol, 1.0 equiv.), $Pd(OAc)_2$ (2.2 mg, 0.010 mmol, 0.10 equiv.) and ^{t}BuPyOx **3.5** (2.1 mg, 0.011 mmol, 0.11 equiv.) in DMF (1 mL) under an atmosphere of O_2 (balloon) at 40 °C for 72 h. The resulting crude was purified by silica gel column chromatography (petroleum ether/EtOAc 10:1) and the CSP-HPLC analysis carried out at this stage. Further purification was then carried out by recrystallisation with DCM/hexanes to removed unknown impurities to yield **3.3ch** (30.2 mg, 0.067 mmol, 67%, >20:1 d.r., 96:4 e.r.) as an off-white powder.

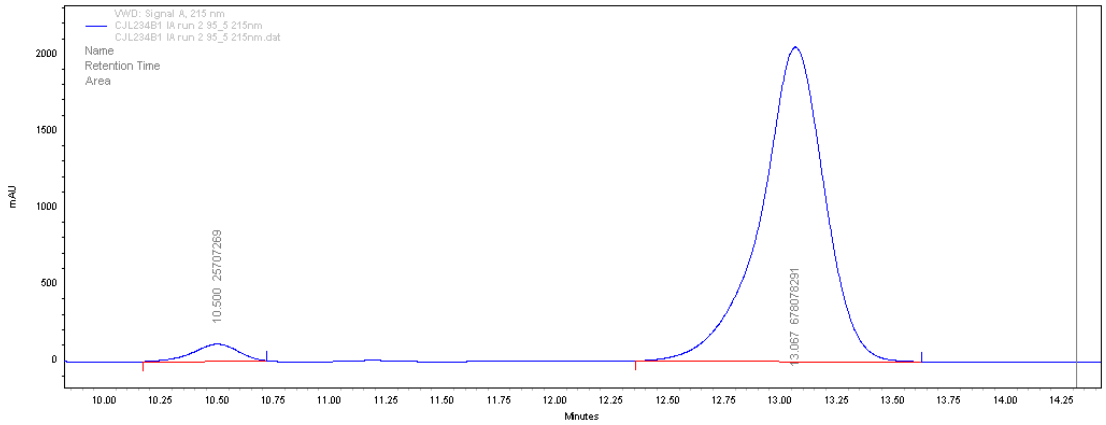
Mp: 158-162 °C (hexanes/DCM); R_f: 0.2 in 10:1 petroleum ether:EtOAc; ν_{max}/ cm^{-1}: 2957, 2927, 1699, 1606, 1510, 1488, 1223, 840, 776, 720 699 ;^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 – 7.18 (m, 3H, Ar-H), 7.17 – 7.11 (m, 3H, Ar-H), 7.02 (m, 4H, Ar-H), 6.98 – 6.91 (m, 2H, Ar-H), 6.91 – 6.83 (m, 2H, Ar-H), 3.92 (dd, *J* = 11.3, 5.0 Hz, 1H, C<u>H</u>Ar), 3.31 (d, *J* = 9.8 Hz, 1H, CH), 3.22 (d, *J* = 9.8 Hz, 1H, CH), 3.05 (dd, *J* = 15.9, 11.3 Hz, 1H, C<u>H</u>H), 2.79 (dd, *J* = 15.9, 5.0 Hz, 1H, CH<u>H</u>), 1.85 (d, *J* = 8.5 Hz, 1H, C<u>H</u>H), 1.64 (s, 3H, CH_3), 1.61 (d, *J* = 8.5 Hz, 1H, CH<u>H</u>), 1.53 (s, 3H, CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ -114.67 (m, F-Ar); ^{13}C NMR (75 MHz, $CDCl_3$) 208.6 (C), 207.9 (C), 162.3 (C) (d, *J* = 246.7 Hz), 147.6 (C), 146.5 (C), 135.6 (C), 135.3 (C), 131.89 (C) (d, *J* = 3.3 Hz), 129.85 (CH) (d, *J* = 8.1 Hz), 129.2 (CH), 128.3 (CH), 128.2 (CH), 127.2 (CH), 127.1 (CH), 115.91 (CH) (d, *J* = 21.4 Hz), 66.1 (CH_2), 60.4 (CH), 59.2 (CH), 58.3 (C), 58.1 (C), 51.8 (CH), 45.8 (CH_2), 19.2 (CH_3), 18.6 (CH_3), one overlapping CH signal; δ HRMS (p NSI) *m/z calc.* for $C_{31}H_{27}FO_2NH_4$: 468.2333 $[M+NH_4]^+$; found: 468.2324; $[\alpha]_D^{20.3}$ = +12.0 (*c* 0.67, $CHCl_3$); 96:4 e.r.; HPLC (CHIRALPAK IA,

hexane/2-propanol: 95:5, flow rate: 1.0 mL min^{-1}, detection UV 215 nm, 25 °C) t_R of major isomer: 13.067 min, t_R of minor isomer: 10.500 min.



VWD: Signal A, 215 nm Results

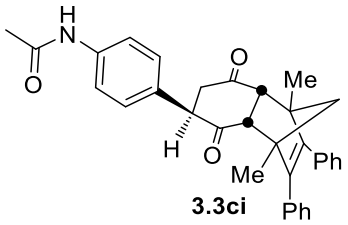
Retention Time	Area	Area %	Height	Height %
10.442	101496789	49.37	3774845	51.96
13.073	104084098	50.63	3489442	48.04
Totals	205580887	100.00	7264287	100.00



VWD: Signal A, 215 nm Results

Retention Time	Area	Area %	Height	Height %
10.500	25707269	3.65	1862106	5.13
13.067	678078291	96.35	34419067	94.87
Totals	703785560	100.00	36281173	100.00

1,4-Dimethyl-5,8-dioxo-2,3-diphenyl-1,4,4a,5,6,7,8,8a-octahydro-1,4-methanonaphthalen-6-yl)phenyl)acetamide 3.3ci



3.3ci

Racemic procedure:

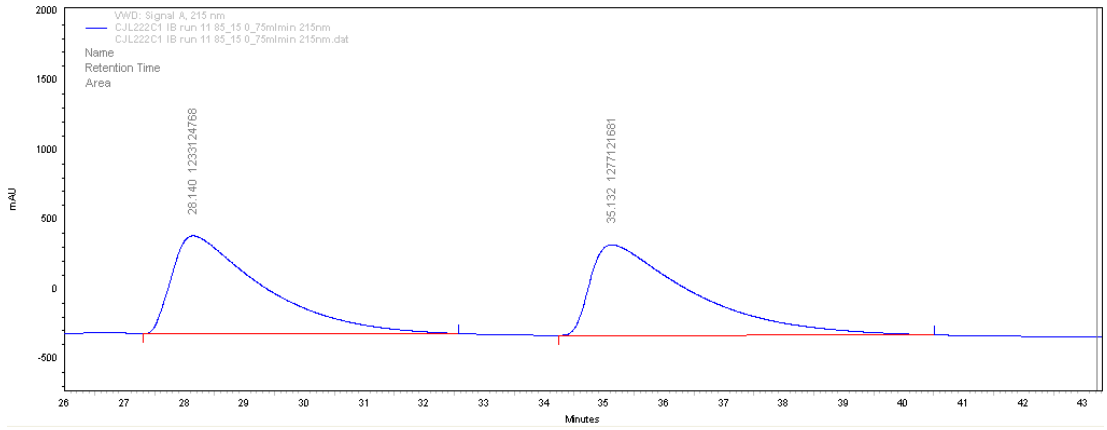
General racemic procedure was followed with modifications, reacting *p*-acetamidophenyl boronic acid **3.2i** (42.9 mg, 0.24 mmol, 2.4 equiv.), Diels-Alder adduct **3.1c** (35.4 mg, 0.099 mmol, 1.0 equiv.), $Pd(OAc)_2$ (1.1 mg, 0.005 mmol, 0.05 equiv.) and 1,10-phenanthroline **3.17** (1.1 mg, 0.006 mmol, 0.06 equiv.) in DMF (1 mL) under an atmosphere of O_2 (balloon) at 50 °C for 72 h. The resulting crude was purified by silica gel column chromatography (petroleum ether:EtOAc 2:1 → 1:1) to yield **3.3ci** (37.5 mg, 0.06 mmol, 69%, >20:1 d.r.) as a colourless amorphous solid with 10% impurities.

Enantioselective procedure:

General enantioselective procedure B was followed with modifications, reacting *p*-acetamidophenyl boronic acid **3.2i** (42.9 mg, 0.24 mmol, 2.4 equiv.), Diels-Alder adduct **3.1c** (35.4 mg, 0.099 mmol, 1.0 equiv.) $Pd(OAc)_2$ (2.2 mg, 0.010 mmol, 0.10 equiv.) and ^{t}BuPyOx **3.5** (2.1 mg, 0.011 mmol, 0.11 equiv.) in DMF (1 mL) under an atmosphere of O_2 (balloon) at 40 °C for 96.5 h. The resulting crude was purified by silica gel column chromatography (hexane:EtOAc 2:1 → 1:1), then recrystallised from DCM/hexanes to remove unknown impurities (after enantiomeric ratio was recorded) and to yield **3.3ci** (20.6 mg, 0.042 mmol, 42%, >20:1 d.r., 98:2 e.r.) as a white powder.

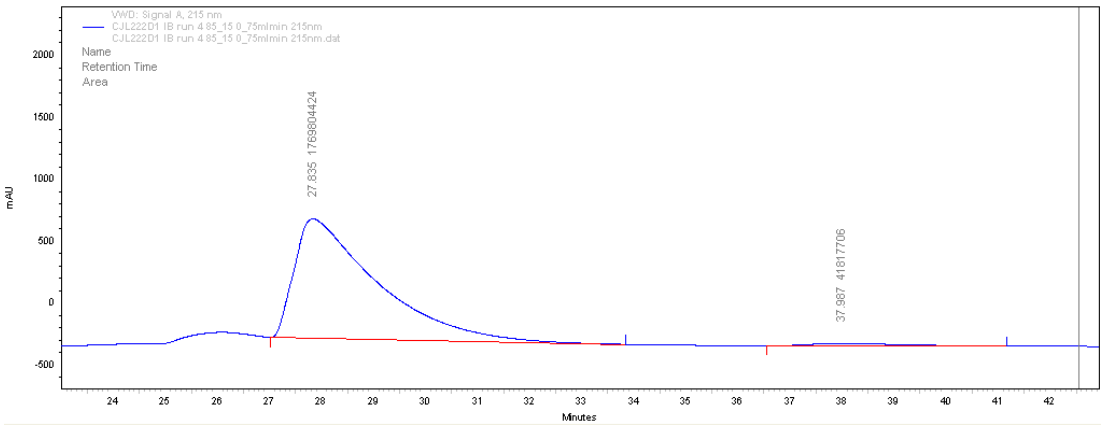
Mp: 114-117 °C (DCM/hexanes); R_f: 0.2 in 2:1 petroleum ether:EtOAc; ν_{max}/ cm^{-1}: 3311, 1694, 1600, 1516, 1443, 1411, 745, 726, 698; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50

– 7.41 (m, 3H, Ar-H), 7.23 – 7.11 (m, 6H, Ar-H), 7.05 – 6.97 (m, 2H, Ar-H), 6.97 – 6.91 (m, 2H, Ar-H), 6.90 – 6.84 (m, 2H, Ar-H), 3.90 (dd, *J* = 10.4, 5.1 Hz, 1H, CHAr), 3.29 (d, *J* = 9.9 Hz, 1H, CH), 3.20 (d, *J* = 9.9 Hz, 1H, CH), 3.06 (dd, *J* = 16.0, 10.4 Hz, 1H, CHH), 2.79 (dd, *J* = 16.0, 5.1 Hz, 1H, CHH), 2.14 (s, 3H, $NCOCH_3$), 1.84 (d, *J* = 8.6 Hz, 1H, CHH), 1.62 (s, 3H, CH_3), 1.59 (d, *J* = 8.6 Hz, 1H, CHH), 1.54 (s, 3H, CH_3), overlapping NH signal within the aromatic region; ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.7 (C), 208.5 (C), 168.5 (C), 147.3 (C), 146.7 (C), 137.5 (C), 135.6 (C), 135.3 (C), 131.8 (C), 129.3 (CH), 129.2 (CH), 128.7 (CH), 128.3 (CH), 128.2 (CH), 127.1 (CH), 120.3 (CH), 66.1 (CH_2), 60.2 (CH), 59.1 (CH), 58.1 (C), 58.1 (C), 52.2 (CH), 45.3 (CH_2), 24.7 (CH_3), 19.1 (CH_3), 18.7 (CH_2), and 1 × overlapping CH signal; δ HRMS (FTMS + p NSI) *m/z calc.* for $C_{33}H_{31}NO_3NH_4$: 507.2642 $[M+NH_4^+]+$; found: 507.2637; $[\alpha]_D^{21.5}$ = +27.3 (c 0.37, $CHCl_3$); 98:2 e.r.; HPLC (CHIRALPAK IB, hexane/2-propanol: 85:15, flow rate: 0.75 mL min^{-1}, detection UV 215 nm, 25 °C) t_R of major isomer: 27.835 min, t_R of minor isomer: 37.987 min.



VWD: Signal A, 215 nm Results

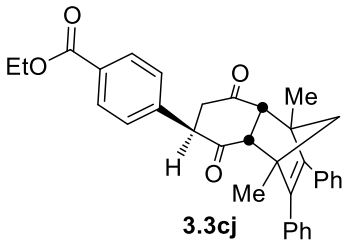
Retention Time	Area	Area %	Height	Height %
28.140	1233124768	49.12	11772886	51.89
35.132	1277121681	50.88	10914042	48.11
Totals	2510246449	100.00	22686928	100.00



VWD: Signal A, 215 nm Results

Retention Time	Area	Area %	Height	Height %
27.835	1769804424	97.69	16156114	97.96
37.987	41817706	2.31	335909	2.04
Totals	1811622130	100.00	16492023	100.00

Ethyl 4-(1,4-dimethyl-5,8-dioxo-2,3-diphenyl-1,4,4a,5,6,7,8,8a-octahydro-1,4-methanonaphthalen-6-yl)benzoate 3.3cj



3.3cj

Racemic procedure:

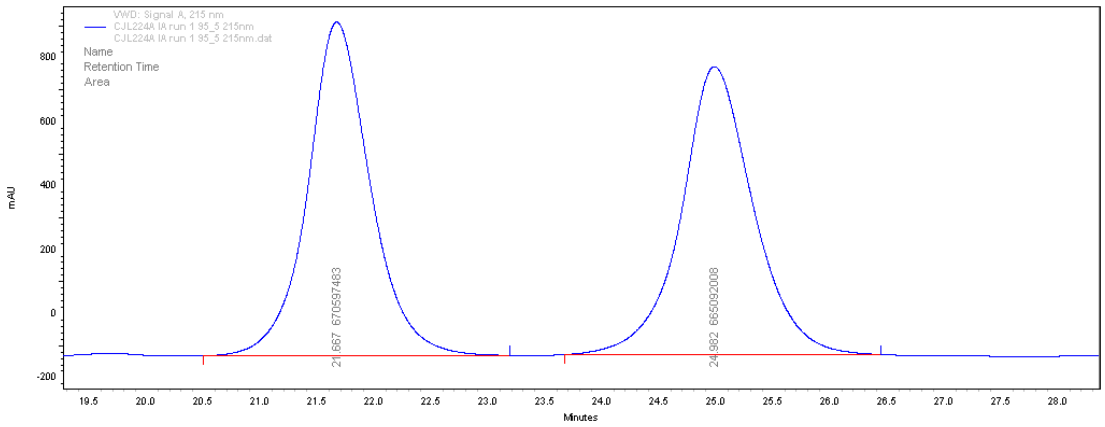
General racemic procedure was followed with modifications, reacting *p*-ethoxycarbonylphenyl boronic acid **3.2j** (46.6 mg, 0.24 mmol, 2.4 equiv.), Diels-Alder adduct **3.1c** (35.4 mg, 0.099 mmol, 1.0 equiv.), $Pd(OAc)_2$ (1.1 mg, 0.005 mmol, 0.05 equiv.) and 1,10-phenanthroline (1.1 mg, 0.006 mmol, 0.06 equiv.) in DMF (1 mL) under an atmosphere of O_2 (balloon) at 50 °C for 72 h. The resulting crude was purified by silica gel column chromatography (petroleum ether:EtOAc 5:1 + 10% toluene). Phenol was removed by sat. K_2CO_3 wash (3 × 10 mL) to yield **3.3cj** (22.8 mg, 0.06 mmol, 45%, >20:1 d.r.) as a colourless amorphous solid.

Enantioselective procedure:

General enantioselective procedure B was followed with modifications, reacting *p*-ethoxycarbonylphenyl boronic acid **3.2j** (42.9 mg, 0.24 mmol, 2.4 equiv.), Diels-Alder adduct **3.1c** (35.4 mg, 0.099 mmol, 1.0 equiv.), $Pd(OAc)_2$ (1.1 mg, 0.005 mmol, 0.005 equiv.) and ^{t}BuPyOx **3.5** (1.2 mg, 0.006 mmol, 0.06 equiv.) in DMF (1 mL) under an atmosphere of O_2 (balloon) at 50 °C for 24 h. An additional portion of $Pd(OAc)_2$ (1.1 mg, 0.005 mmol, 0.05 equiv.), ^{t}BuPyOx **3.5** (1.2 mg, 0.006 mmol, 0.06 equiv.) p-ethoxycarbonylphenyl boronic acid **3.2j** (37.8 mg, 0.20 mmol, 2.0 equiv.) was added and the reaction was stirred at 50 °C under an atmosphere of O_2 (balloon) for 48 h (72 h total). The reaction was diluted with 2:1 Et_2O:EtOAc (15 mL) and washed with sat. K_2CO_3 (3 × 10 mL), water (2 × 10 mL), brine (10 mL) and dried over $MgSO_4$. Solvent was removed under reduced pressure. The resulting crude was purified by silica gel column chromatography (hexane:EtOAc 10:1 → 5:1) to yield **3.3cj** (6.6 mg, 0.013 mmol, 13%, >20:1 d.r., 95:5 e.r.) as an off-white amorphous solid.

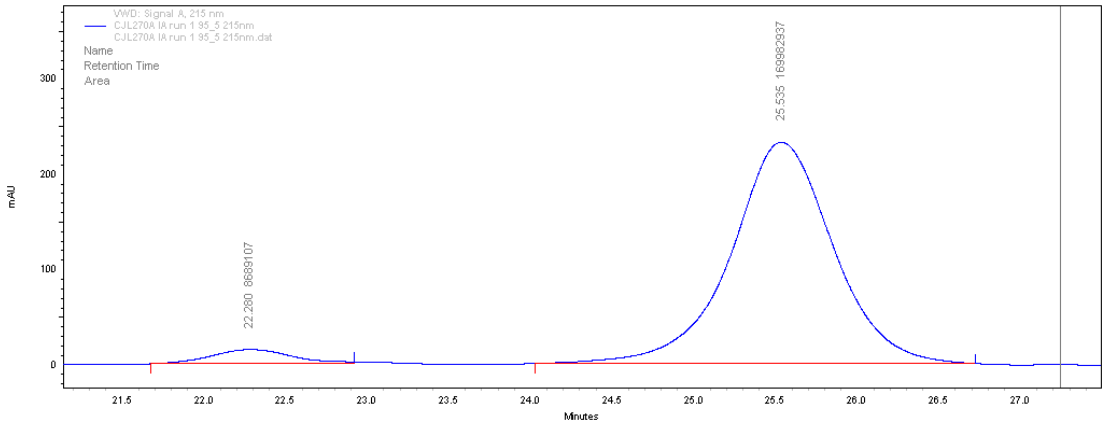
R_f: 0.2 in 5:1 petroleum ether:EtOAc; ν_{max}/ cm^{-1}: 2958, 2927, 2870, 1701, 1699, 1524, 1488, 1443, 1275, 1181, 1105, 1021, 800, 728, 698; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 – 7.89 (m, 2H, Ar-H), 7.17 – 6.99 (m, 8H, Ar-H), 6.92 – 6.75 (m, 4H, Ar-H), 4.30 (q, *J* = 7.1 Hz, 2H, C<u>H</u>$_2$CH$_3$), 3.92 (dd, *J* = 11.6, 5.1 Hz, 1H, C<u>H</u>Ar), 3.25 (d, *J* = 9.9 Hz, 1H, CH), 3.16 (d, *J* = 9.9 Hz, 1H, CH), 3.03 (dd, *J* = 15.9, 11.6 Hz, 1H, C<u>H</u>H), 2.73 (dd, *J* = 15.9, 5.1 Hz, 1H, CH<u>H</u>), 1.78 (d, *J* = 8.6 Hz, 1H, C<u>H</u>H), 1.57 (s, 3H, CH_3), 1.53 (d, *J* = 8.6 Hz, 1H, CH<u>H</u>), 1.45 (s, 3H, CH_3), 1.31 (t, *J* = 7.1 Hz, 3H, CH_2C<u>H</u>$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.1 (C), 207.5 (C), 166.3 (C), 147.7 (C), 146.4 (C), 141.1 (C), 135.6 (C), 135.2 (C), 130.2 (CH), 130.0 (C), 129.25 (CH), 129.23 (CH), 128.35 (CH), 128.32 (CH), 128.2 (CH), 127.2 (CH), 66.1 (CH_2), 61.2 (CH_2), 60.4 (CH), 59.4 (CH), 58.4 (C), 58.1 (C), 52.5 (CH), 45.5 (CH_2), 19.2 (CH_3), 18.5 (CH_3), 14.5 (CH_3), 1 ×

overlapping CH signal; HRMS (TOF MS ASAP +) *m/z calc*. for $C_{34}H_{31}O_4$: 203.2222 $[M\text{-}H]^+$; found: 503.2223; $[\alpha]_D^{22.3}$ = +21.7 (c 0.5, $CHCl_3$); 95:5 e.r.; HPLC (CHIRALPAK IA, hexane/2-propanol: 95:5, flow rate: 1.00 mL min^{-1}, detection UV 215 nm, 25 °C) t_R of major isomer: 25.535 min, t_R of minor isomer: 22.280 min.



VWD: Signal A, 215 nm Results

Retention Time	Area	Area %	Height	Height %
21.667	670597483	50.21	17500431	53.67
24.982	665092008	49.79	15106659	46.33
Totals	1335689491	100.00	32607090	100.00

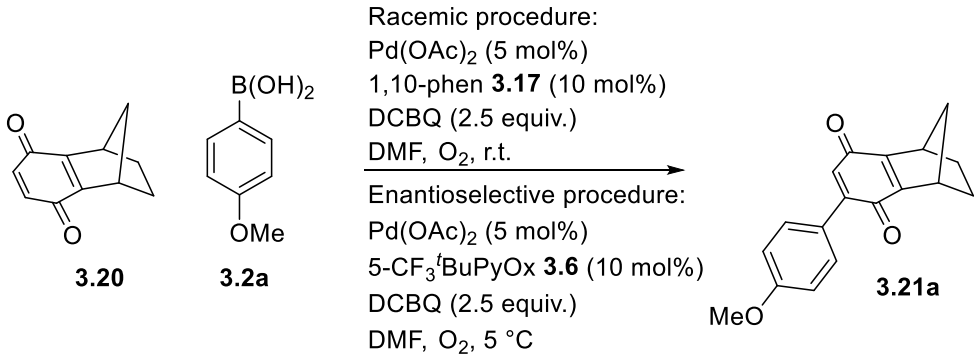


VWD: Signal A, 215 nm Results

Retention Time	Area	Area %	Height	Height %
22.280	8689107	4.86	249849	6.02
25.535	169982937	95.14	3898254	93.98
Totals	178672044	100.00	4148103	100.00

3.9.6 Quinone products

6-(4-Methoxyphenyl)-1,2,3,4-tetrahydro-1,4-methanonaphthalene-5,8-dione 3.21a



Racemic procedure:

Quinone **3.20** (17.7 mg, 0.10 mmol, 1.0 equiv.) and *p*-methoxyphenyl boronic acid **3.2a** (37.3 mg, 2.5 mmol, 2.5 equiv.) were added to the reaction flask along with $Pd(OAc)_2$ (1.1 mg, 0.005 mmol, 0.05 equiv.), 1,10-phenanthroline **3.17** (1.8 mg, 0.01 mmol, 0.1 equiv.), DCBQ (44.2 mg, 0.25 mmol, 2.5 equiv.) and DMF (1 mL). The resulting mixture was stirred at room temperature, under an atmosphere of O_2 (balloon) for 16 h. The reaction mixture was diluted with 2:1 Et_2O:EtOAc (15 mL) and washed with H_2O

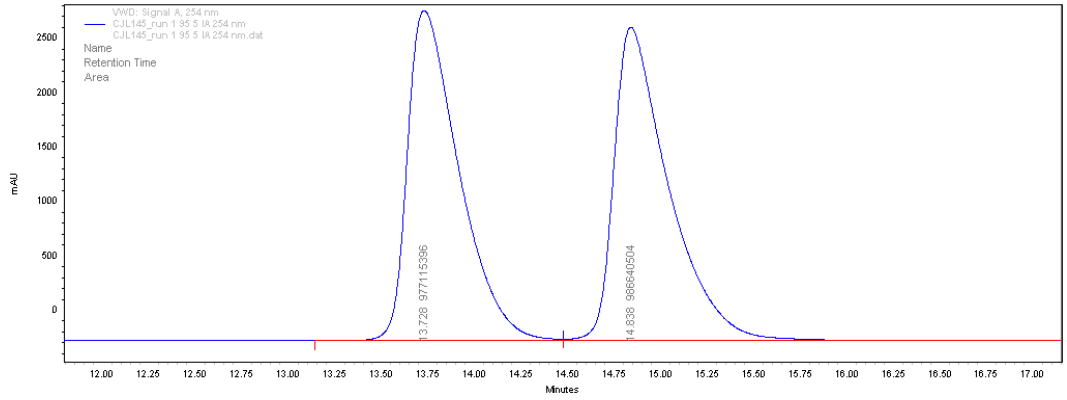
(3 × 10 mL) and brine (1 × 10 mL). The combined organic layers were dried over $MgSO_4$ and solvent was removed under reduced pressure. The resulting crude product was purified by silica gel column chromatography (10:1 petroleum ether:EtOAc) to yield **3.21a** (24.5 mg, 0.084 mmol, 84%) as a bright orange oil.

Enantioselective procedure:

Quinone **3.20** (17.4 mg, 0.099 mmol, 1.0 equiv.) and *p*-methoxyphenyl boronic acid **3.2a** (37.5 mg, 2.5 mmol, 2.5 equiv.) were added to the reaction flask along with $Pd(OAc)_2$ (1.1 mg, 0.005 mmol, 0.05 equiv.), 5-CF_3-^{t}BuPyOx **3.5** (2.7 mg, 0.01 mmol, 0.1 equiv.), DCBQ (44.5 mg, 0.25 mmol, 2.5 equiv.) and DMF (1 mL). The reaction was stirred at room temperature, under an atmosphere of O_2 (balloon) for 25 h. The reaction mixture was diluted with 2:1 Et_2O:EtOAc (15 mL) and washed with H_2O (3 × 10 mL) and brine (1 × 10 mL). The combined organic layers were dried over $MgSO_4$ and solvent was removed under reduced pressure. The resulting crude was purified by silica gel column chromatography (10:1 hexanes:EtOAc) to yield **3.21a** (27.0 mg, 0.096 mmol, 96%, 63:37 e.r.) as a bright orange oil.

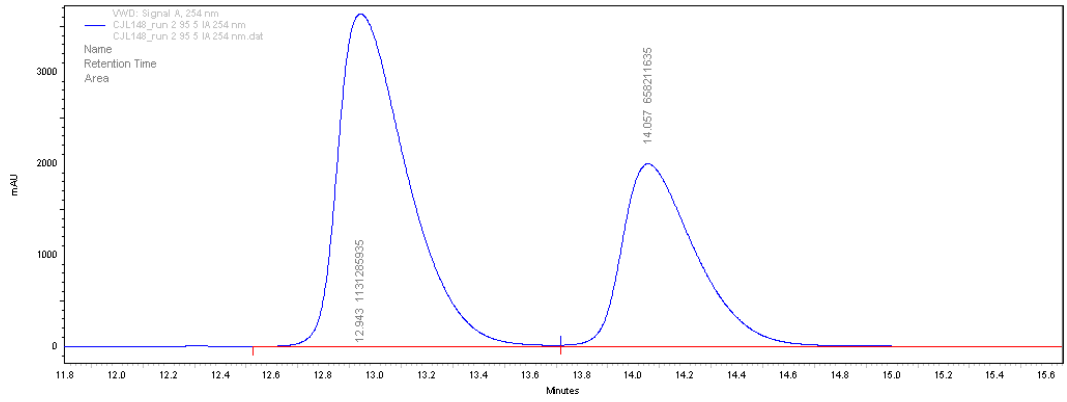
R_f: 0.28 in 10:1 petroleum ether:EtOAc; ν_{max}/ cm^{-1}: 2965, 2867, 2841, 1644, 1599, 1579, 1562, 1449, 1089, 1030, 1015, 835, 798, 724; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.9 Hz, 2H, Ar-H), 6.94 (d, *J* = 8.9 Hz, 2H, Ar-H), 6.61 (s, 1H, =CH), 3.84 (s, 3H, OCH_3), 3.57 – 3.53 (m, 1H, CH), 3.53 – 3.50 (m, 1H, CH), 2.00 – 1.89 (m, 2H, CH_2), 1.73 – 1.64 (m, 1H, C<u>H</u>H), 1.42 (dt, *J* = 9.1, 1.4 Hz, 1H, CH<u>H</u>), 1.27 – 1.18 (m, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.8 (C), 184.3 (C), 161.2 (C), 151.9 (C), 151.6 (C), 145.4 (C), 131.2 (CH), 131.0 (CH), 125.8 (C), 114.1 (CH), 55.5 (CH_3), 47.9 (CH_2), 41.2 (CH), 40.8 (CH), 25.32 (CH_2), 25.27 (CH_2); HRMS (FTMS + p NSI) *m/z calc.* for $C_{18}H_{17}O_3$: 281.1172 $[M+H]^+$; found: 281.1175; $[\alpha]_D^{21.0}$ = -32.0 (*c* 1.0, $CHCl_3$); 63:37 e.r.; HPLC (CHIRALPAK IA, hexane/2-propanol: 95:5, flow rate: 1.0 mL min^{-1},

detection UV 254 nm, 25 °C) t_R of major isomer: 13.832 min, t_R of minor isomer: 15.015 min.



VWD: Signal A, 254 nm Results

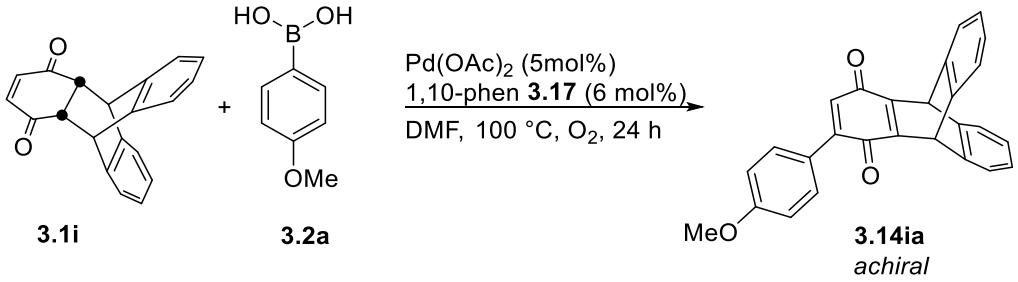
Retention Time	Area	Area %	Height	Height %
13.728	977115396	49.76	50932908	51.30
14.838	986640504	50.24	48360082	48.70
Totals	1963755900	100.00	99292990	100.00



VWD: Signal A, 254 nm Results

Retention Time	Area	Area %	Height	Height %
12.943	1131285935	63.22	60949290	64.55
14.057	658211635	36.78	33475151	35.45
Totals	1789497570	100.00	94424441	100.00

14-(4-Methoxyphenyl)-9,10-dihydro-9,10-[1,2]benzenoanthracene-13,16-dione 2.27a



3.1i **3.2a** **3.14ia** *achiral*

Diels-Alder adduct **3.1i** (28.4 mg, 0.10 mmol, 1.0 equiv.) and *p*-methoxyphenyl boronic acid **3.2a** (38.4 mg, 2.5 mmol, 2.5 equiv.) were added to the reaction flask along with $Pd(OAc)_2$ (1.1 mg, 0.005 mmol, 0.05 equiv.), 1,10-phenanthroline **3.17** (0.9 mg, 0.05 mmol, 0.05 equiv.), and DMF (1 mL). The reaction was stirred at 100 °C, under an atmosphere of O_2 (balloon) for 24 h. The mixture was diluted with 2:1 Et_2O:EtOAc (15 mL) and washed with H_2O (3 × 10 mL) and brine (1 × 10 mL). The combined organic layers were dried over $MgSO_4$ and solvent was removed under reduced pressure. The resulting crude was purified by silica gel column chromatography (10:1 hexane:EtOAc) to yield **3.14a** (16.7 mg, 0.043 mmol, 43%) as a bright orange oil.

R_f: 0.4 in 5:1 petroleum ether:EtOAc; ν_{max}/ cm^{-1}:2930, 2835, 1655, 1641, 1619, 1598, 1580, 1509, 1456, 1267, 1254, 1176, 1030, 832, 752; ^1H NMR (300 MHz, $CDCl_3$) δ 7.49 – 7.42 (m, 4H, Ar-H), 7.39 (d, *J* = 8.9 Hz, 2H, Ar-H), 7.08 – 7.01 (m, 4H, Ar-H), 6.93 (d, *J* = 8.9 Hz, 2H, Ar-H), 6.63 (s, 1H, =CH), 5.88 (s, 1H, CH), 5.84 (s, 1H, CH), 3.84 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.8 (C), 183.5 (C), 161.4 (C), 152.2 (C), 152.0 (C), 144.8 (C), 144.1 (C), 144.0 (C), 131.0 (CH), 130.3 (CH), 125.73 (CH), 125.69 (CH), 125.5 (C), 124.6 (CH), 124.5 (CH), 114.2 (CH), 55.5 (CH_3), 48.0 (CH), 47.5 (CH); HRMS (FTMS + p NSI) *m/z calc.* for $C_{27}H_{19}O_3$: 391.1329.1172 $[M+H]^+$; found: 391.1331.

3.10 References

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Appendix I: Racemic Anthracene Diels-Alder Adduct Studies

Appendix I goes into more detail about the research discussed in Chapter 3 regarding the distinctive reactivity of anthracene Diels-Alder adduct **3.1i.** As such the numbering has been kept consistent with Chapter 3 for clarity.

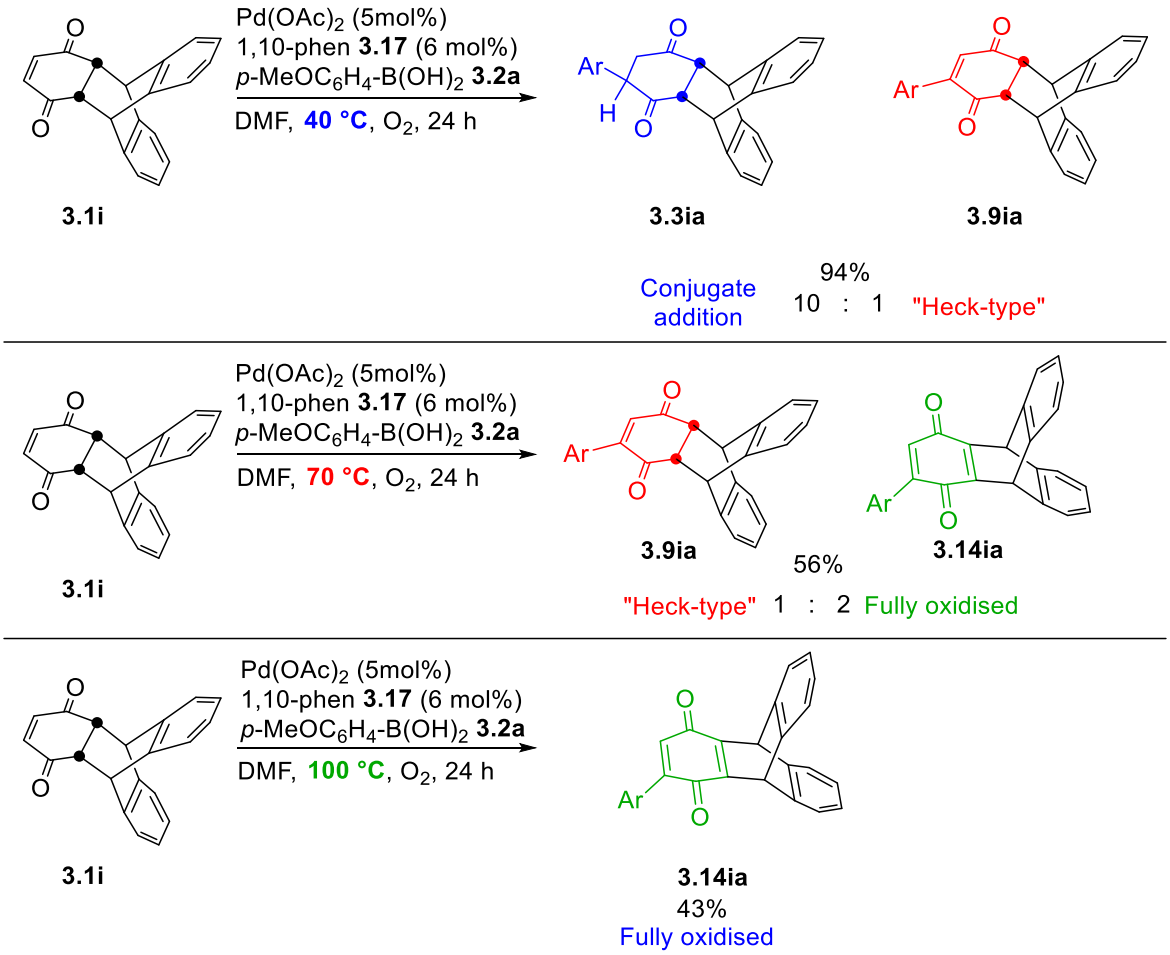
As briefly mentioned in Chapter 3, Section 3.4.3.3, anthracene Diels-Alder adduct **3.1i** behaved quite differently under our Pd(II)-catalysed conjugate addition conditions with respect to the other Diels-Alder adducts screened.

To try and garner more information about the unique reactivity of **3.1i**, we carried out several racemic coupling reactions at various temperatures (Scheme I.1). The racemic studies were performed with *p*-methoxyphenyl boronic acid **3.2a,** however, in order to record the enantioselectivity of the reaction we had to switch to *p*-hydroxyphenyl boronic acid **3.2d** for chiral stationary phase HPLC separating conditions. Firstly, **3.1i** is the only substrate in which we were able to access the oxidative Heck coupled product **3.9ia** under both racemic conditions and enantioselective conditions. Interestingly, under racemic conditions with 1,10-phen **3.17**, conjugate addition product **3.3ia** is favoured at room temperature. However, using ^{t}BuPyOx **3.5**, the oxidative Heck product **3.9ai** becomes more favourable. Control reactions were carried out (as documented in Chapter 3, Section 3.5.2) which proved that the oxidative Heck product **3.9ia** is the result of a true oxidative Heck reaction and not conjugate addition followed by oxidation. Secondly, **3.1i** is the only substrate where we were able to isolate the coupled benzoquinone product **3.14ia**, which we believe is formed through the oxidation of Heck-type product **3.9ia**.

The conjugate addition **3.3ai** and the oxidative Heck **3.9ia** products of anthracene Diels-Alder adduct **3.1i** are both chiral molecules, as the addition of the aryl group to the

enedione breaks the mirror plane in the molecule. However, the additional oxidation to form benzoquinone **3.14ia** from the chiral oxidative Heck product **3.9ia** introduces a new place of symmetry perpendicular to the plane originally broken so, unfortunately, **3.14ia** is achiral (Figure I.1).

We were able to control the synthesis of the conjugate addition product **3.3i** (through conditions B, see Chapter 3, Section 3.4.3.3) and the synthesis of coupled benzoquinone **3.14ia** by increasing the reaction temperature to 100 °C force oxidation, albeit in a poor yield of 43% (Scheme I.1). At this increased reaction temperature, we observed retro-Diels-Alder products which is perhaps the reason why the yield could not be improved. However, we were never able to selectively furnish the oxidative Heck product **3.9ia** through our Pd(II)-catalysed protocol (Chapter 3, Section 3.4.3.3 and Appendix I, Scheme I.1). As the control reaction in Chapter 3, Section, 3.5.2 points to the reaction being true oxidative Heck and not conjugate addition followed by oxidation, this explains why the yield of oxidative Heck could not be improved by leaving the reaction longer.



Scheme I.1: Racemic coupling reactions at various temperatures

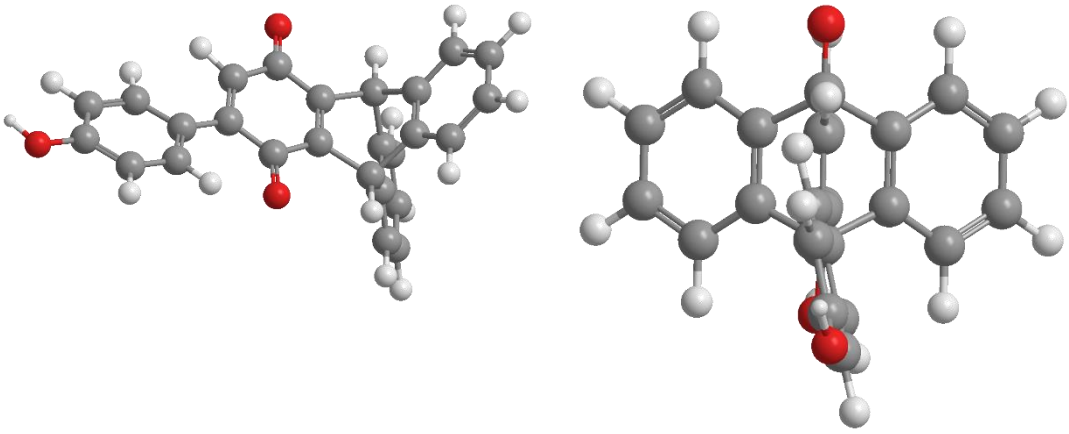


Figure I.1: Chem3D structure of benzoquinone **3.14ia**, and plane of symmetry of **3.14ia**

Appendix II: List of Publications

Auto-Tandem Catalysis: Pd(II)-Catalysed Dehydrogenation/Oxidative Heck of Cyclopentane-1,3-diones

C. J. C. Lamb, B. G. Nderitu, G. McMurdo, J. M. Tobin, F. Vilela, A.-L. Lee, *Chem. Eur. J.*, 2017, **23**, 18282-18288

Pd(II)-Catalyzed Enantioselective Desymmetrization of Polycyclic Cyclohexenediones: Conjugate Addition versus Oxidative Heck

C. J. C. Lamb, F. Vilela and A.-L. Lee, *Org. Lett.*, 2019, **21**, 8689-8694